A HISTORY
OF TROPICAL MEDICINE

Based on

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BY

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CHAPTER XI

CHOLERA

1. GENERAL ACCOUNT

Of all pestilences cholera is perhaps the most awe-inspiring; it may run so rapid a course that a man in good health at daybreak may be dead and buried ere nightfall. Again and again has the fear of cholera been the beginning of sanitary wisdom. Incidentally, Public Health legislation in Great Britain owed much in its earliest days to cholera. It was not a medical man, but a lawyer-sanitarian, Sir Edwin Chadwick (1800–90), who was chiefly responsible for initiating the public health era, and it was largely through his efforts that the Public Health Act of 1848 came into existence. He was helped in attaining his ends by outbreaks of cholera in England which brought home to Englishmen the dangers to which their fellow-countrymen and others abroad, in India and the Colonies, were exposed at all times. A General Board of Health was established but met at first with no little opposition because it conflicted with vested interests and because local authorities resented central·control—we see the same in some colonies to-day. The Board survived for ten years only, but did good work, for, as one result, Liverpool appointed a Medical Officer of Health, and was the first city to do so, and soon afterwards John Simon was appointed to the corresponding position for London.

It was cholera that helped the Sanitary Act of 1866 to become law and in consequence a more sanitary atmosphere began to prevail. A cholera survey yielded much information as to the sanitary state of many districts and the means employed to prevent infection entering from abroad.

In Chadwick's day the surroundings amid which the poorer people lived were highly insanitary and favoured the spread of cholera when once it was introduced. Seeing that cholera is one of those diseases which formerly were much more widespread and occurred commonly in temperate climates—but is now of a limited distribution and mainly a disease of warm climates—it will be

instructive to glance for a moment at the conditions in England a century or so ago when the disease was raging there and we shall see that they were similar to those associated with the disease abroad at the present time, and it is but natural to infer that measures which have resulted in freeing Great Britain from cholera in the past will, if applicable and applied abroad, *mutatis mutandis*, have the like happy results.

In the eighteen-thirties cholera was raging in Bethnal Green and 'summer-houses' in the gardens of weavers were occupied as dwellings, though situated on undrained soil and with mere holes in the ground for privies, while the water-supply was obtained from surface wells into which the refuse and ordure from the houses gained entrance. Larger houses were tenement dwellings in which an entire family might live in a single room, and since the ordinary privies were very soiled and dirty and, moreover, access to them implied exposure, the excreta were often kept, temporarily at least, in the room until the atmosphere became almost unbearable.

A few years later, in 1847, Lambeth had common sewers, but most of the houses had no drains leading to them, and even the large houses had cesspools only. Further, many of the so-called sewers were little more than elongated cesspools, the water-supply was inadequate to flush them, they might overflow and their contents come up through untrapped gullies. In October the following year the Common Council of the City of London met and a recommendation of the Commissioners of Sewers was passed after much discussion, that a medical officer of health should be appointed for the City and Liberties of London forthwith to hold office till January, that was for three months. He was to be paid £150 for this. Who was appointed we have not been able to find out, but a few days later the Lord Mayor reported that every effort was being made by the Commissioners of Sewers to enforce the sanitary recommendations of the Board of Health and that he had received a letter from Dr. J. A. Paris, President of the Royal College of Physicians, informing him to his great satisfaction that the College had appointed a Standing Committee to consider the subject of cholera.

It is not within the scope of these lectures to discuss whether the χολέρα of Hippocrates (460–370 B.C.) or the disease so called by Celsus, who lived in the reign of Tiberius, or, again, that described some eighty years later by Cœlius Aurelianus, by Aretæus of Cappadocia and other ancient medical writers was the same as

Cholera asiatica (should it not rather be named *indica* ?) of modern times. We may certainly take it that ξηρα χολέρα of Hippocrates had nothing to do with cholera as we know it, for the term was used for obstinate obstruction, not intractable diarrhœa. The etymologically corresponding Latin term *cholera sicca* is used in modern text-books for a very fatal type of the disease in which the patient succumbs to an overwhelming dose of poison and dies in a few hours without any reaction or symptoms of diarrhœa, vomiting.

Apart from Hippocrates and Roman medical authors, it is mentioned in Chinese and Hindu writings. The first European writer in more modern times to describe it was Bontius or Bonsseus, a physician to the Dutch East India Company, in Batavia in 1629.

Medical records of historical value may be taken as starting from what is known as the First Pandemic of the early years of the nineteenth century, though the earliest description of the disease in epidemic form was probably the outbreak which devastated Ahmed Shad's military forces in A.D. 1438.

Four such pandemics occurred during the century: the first from 1817–23, the second from 1826–37, the third from 1846–63, and the fourth from 1865–75. The first is always spoken of as starting in 1817 because reliable information of the dates of its diffusion begin at Kishnagur on the Hooghly in May that year; there is little doubt, however, that in 1816 cholera was already becoming endemic in Behar. There is no need to describe its extension in detail or its ravages in the different districts attacked; suffice it to say that by 1818 infection had crossed the borders to invade Ceylon in 1819, then Mauritius and on to East Africa in 1820, the Philippines, China and Japan in 1822. In another direction it passed to Arabia in 1821, thence, in 1822, to Persia and Syria, and in 1823 Russia. Briefly, in this period it had extended over a territory of nearly a hundred degrees of longitude, from Nagasaki in 147° East to the coast of Syria in 52° East, and upwards of sixty-seven degrees of latitude, from Bourbon (now known as Réunion) in 21° South to Astrakhan in 46° 21' North. This pandemic, it will be observed, did not cross the frontiers of Europe, though it came very close.

Professor Major Greenwood, when speaking of the difference between this pandemic of 1817 and outbreaks of the three preceding centuries in his work on *Epidemic and Crowd Diseases*, a work full of interest, of instruction and of stimulating ideas, says: " This difference may be summarized in a phrase as a difference

in *dispersiveness* " and quotes the following passage from Georg
Sticker's *Abhandlungen aus der Seuchengeschichte und Seuchenlehre*
(1912) :

Was neu in der Geschichte der Indischen Cholera war und was
die Gemüter dort wie hier mit Recht erregte, war die weitere Nachricht,
dasz jene verherrende Seuche nicht mehr örtlich beschränkt blieb und
zur gewohnten Jahreszeit an vielen Orten zugleich auftrat, sondern
sich in Bewegung setzte, unter einem geheimnisvollen Antriebe zu
wandern begann und ohne Rücksicht auf die Jahreszeit, sich an den
Menschen verkehr von Menschenleben fordernd.   Noch in selben Jahre
einen groszen Teil der Halbinsel erobernd kann sie schon im folgendem
Jahre über die Grenzen Vorderindiens hinaus, durchzog ostwärts und
westwärts die nordlichen Länder Asiens, berührte im Jahre 1823 im
Kaukasus und am Volgaflusz die Grenzen Ruszlands und bedrohte so
Europa.

[What was new in the history of Indian cholera and rightly caused
apprehension there as well as here was the further intelligence that
this destructive epidemic [of 1817] no longer confined itself to a parti-
cular area and at the accustomed season of the year appeared simul-
taneously in several places, but set itself in motion, under the influence
of some mysterious impulse began to travel, and, without paying atten-
tion to the season of the year, attaching itself to the lines of human
intercourse, spread widely in various directions, exacting everywhere
hecatombs of victims.   In that very year a great part of the peninsula
was conquered ;   in the following year cholera crossed the frontier of
Upper India and travelled east and west through the northern lands
of Asia.   By 1823 cholera, in the Caucasus and on the Volga, reached
the frontiers of Russia and thus menaced Europe.]

In order to retain a chronological sequence we will here state
the general opinion relative to this disease at the time of the
first pandemic as given by Leonard Rogers.   Neither the proximate
cause nor the remote causes were known but negative propositions
were affirmed that it was not due to improper food nor to irre-
gularity of seasons, though climatic influences, especially a moist
east wind, might play some part.   The observed route of exten-
sion along rivers was ascribed to commerce.   Since removal of
inhabitants to a new site often ended an outbreak the disease was
believed not to be contagious, and quarantine measures were
regarded as useless.

Reginald Orton held that cholera was " due to deficient nervous
action brought about by a lessened aeration of the blood, which
is itself dependent on unsettled weather consequent on deficient
electrical fluid in the atmosphere "—a view about as enlightening
as Abram's box.

The second pandemic, 1826–37, also started in India and after
the lapse of only three years from the ending of the first.   It

extended over an even larger area and in several directions :
From India to China, from India to Russia, and thence successively
to Poland, Germany, Great Britain and France, to Belgium,
Holland and Norway. It was of this epidemic as Heinrich Heine
saw it in France that he wrote in a letter dated 9th April, 1832,
how on 29th March, the night of *mi-carême*, a masked ball was in
progress when one of the harlequins collapsed with cholera. In
a short while carriage-loads of people were hurried to the Hôtel
Dieu to die, and to prevent a panic they were thrust into rude
graves without even removal of their dominoes. Soon the public
halls were filled with the dead, sewed up in sacks for lack of coffins.
Long lines of hearses stood *en queue* outside Père Lachaise. The
rich fled from the town and over 120,000 passports were issued
at the Hôtel de Ville.

Other parts of the Continent appear to have become infected
viâ Great Britain, rather than directly ; thus Portugal was almost
certainly so invaded and after that Spain, Italy, Sicily and Switzer-
land. From Britain it is probable that Canada was invaded and
thence the United States, Cuba, South and Central America.
This pandemic died down in 1837 and for the next decade no
records of cholera in Europe, Africa or America are found.

During this extensive outbreak quarantine was in force in
various countries but did not avail to prevent the spread of in-
fection ; a triple cordon of troops was instituted and was found
equally useless ; in Spain the death penalty was imposed for
infringement of rules, but it, too, proved futile. At this time the
air-borne theory of propagation gained more adherents. The
influence of climatic variations and chills was believed to play a
large part in initiating outbreaks, but the capriciousness of the
distribution was thought to be due to generation of a poison in
the soil which " checked perspiration, congested the bowels and
led to inflammation." Contagion was not believed to take much
share because it was noticed again and again that those attending
on the sick in hospital did not often contract the disease. During
this period it may be noted from perusal of reports of cases that
copious bleeding found fewer advocates ; also intravenous injec-
tion of salines were first tried—by Latta and Mackintosh (see
later).

The third pandemic, 1846–63, and the fourth, 1865–75, do not
call for any detailed description, the accounts of them would be
very like those already given. Suffice it to say that during the
third, infection spread over the whole northern hemisphere and

to 25° South in the Old World, and to 30° South in the New World. The fourth is particularly noteworthy, first on account of its course, for it passed to Southern Europe by sea from the coast of Arabia instead of the former route *viâ* Afghanistan, Persia and Russia, and second by reason of its unexampled rapidity of spread, taking only a few weeks to reach Europe.   These two are interconnected, the rapidity of spread being brought about by the shorter route to travel.   Since then there have been no such widespread outbreaks.

Sir James Ranald Martin has some interesting remarks on these epidemics and particularly in comparing the rate of spread of the infection in the second and third.   That of 1817 started on the shores of the Ganges, and then passed to the Indus and Euphrates, Nile, Danube, Volga, St. Lawrence and the Mississippi.   Since then, he states, epidemics " have always originated *in* and issued forth *from* India, but not, to my knowledge, been imported into India by ships from infected countries."   Martin held that " communication from person to person was very rare and even when the disease is presumptively contagious, it cannot be localized by quarantine."

The following table shows the spread and its rate in the outbreaks of 1830 and 1847, as regards Russia, Europe and Great Britain.

		1830–1.	1847–8.
Astrakhan	.	1830, 20th July	1847, June
Moscow	.	„ September	„ 18th September
St. Petersburg	.	1831, 16th June	1848, June
Berlin	.	„ 31st August	„ June
Hamburg	.	„ October	„ September
Sunderland	.	„ 24th October	„ 4th October
Edinburgh	.	1832, 22nd January	„ 1st October

It is worthy of note that each successive ' pandemic ' reached a wider distribution than its immediate predecessor, and interesting also to see how certain districts, even countries, escaped. Thus, it did not invade Australia or the Pacific Islands, nor East Africa south of Delagoa Bay, the Cape, the interior and southern parts of Africa to the Sudan, parts of the West Coast of Africa, or St. Helena; in South America, the Falkland Islands, Tierra del Fuego, Patagonia and Chile ; North America above the fiftieth parallel, the Bermudas ; in Europe, Iceland, the Hebrides, Shetland and the Orkneys ; Russia north of the sixty-fourth parallel. No explanation altogether satisfying is found for these exemptions. We can only affirm that India was the home of cholera and that there are certain parts of the globe into which the virus has been

introduced, and more than once, by traffic, but which have, never-theless, not become the sites of outbreaks. This would seem to point to local peculiarities favourable or inimical to endemicity, as Hergt formulated a hundred years ago (1838). *Elevation* was thought to play a part, but this *per se* does not protect. Though, generally speaking, there is a diminution of disease with altitude and high places may remain free when the plains below are suffering severely, nevertheless it may occur at all altitudes and present the same symptomatology. Again, *saturation of soil* with retention of decomposing organic matter has been held to favour the pre-valence and spread, and that diffusion followed the course of rivers was noted in India in the epidemic of 1817 and was observed to progress up-stream as well as down, and so was not ascribable to infection of river water used for drinking. We know now that this is explained by traffic routes.

In this connection mention may be made of Radcliffe who in the middle of last century reported, relative to outbreaks of cholera in England, that

the state of the soil and the degree to which it was charged with moisture and decomposing organic matter, especially excrementitious, has been held to exercise an important influence over the localization of the disease, while over thirty years earlier Gendrin, speaking of Paris outbreaks, noted as " the chief general predisposing cause " . . . the crowding of the inhabitants along the river banks.

The influence of seasons and weather we cannot now consider in detail for their importance cannot be regarded from the his-torical aspect ; attention in this respect may be directed to the investigations of Sir Leonard Rogers who compared outbreaks in various parts of India over a period of forty-five years with the rainfall in those areas. He found that all but one of forty-one epidemics had been preceded by failure of the rains ; also that an unusually early rise of the absolute humidity favoured early recrudescence or spread, and on these lines correct forecasting of epidemics had been made. As regards rainfall, however, two points, apparently opposite, may be noted. In some places, for example Hindustan and at the junction of the Jumna and the Ganges and in Nepaul, epidemic outbreaks, if occurring at unusual seasons, have been found associated with sudden and heavy falls of rain ; in others, as in Bangalore in 1874 and in other parts of the Deccan, unusually copious rains seemed to bring the outbreak to an end. Possibly in the former case the rain helped to dis-seminate the infection, in the latter to wash it away. The char-acter of the soil is, therefore, probably a factor of importance.

The actual *type* of disease appears to be unaffected by latitude or longitude, climate and so forth, but the fatality rate differs in different epidemics ; thus, in India in the first pandemic it varied between 20 and 40 per cent. among European troops according to the locality ; in 1831–8 in the Bombay Presidency it ranged between 33 and 50 per cent. Like other infections diseases, cholera outbreaks may be at one time mild, at another severe, whether due to less concentration of the poison or to climatic or geographical influences cannot be stated.

Individual predisposition, however that may be explained, and peculiarities of race and nationality, food, habitations, mode of life, may each play a part. It has been widely, in fact generally, held that the negro race is very susceptible ; this has been recorded by Christie in East Africa, by Dauban in Mauritius, Petit and Vonson in Réunion, Walther in Guadeloupe, and Aschenfeld in Brazil. On the other hand, again and again the relative immunity of the Sepoys in India has been observed, by Cunningham and Bryden among others, although in those who are attacked the *type* of disease differs in no way from that seen in Europeans. The different modes of living, social conditions, density of population doubtless have some influence, for in certain parts of India, Assam, Siam and Burma where the life of the poor is a hard one the natives suffer more than do the Europeans.

As we did in the cases of the first and second pandemics we may here state briefly the general view held at the time of the 1840–9 outbreak. It was the worst recorded up to that time ; over a million deaths from it were said to have taken place in Russia between 1847 and 1849, and 53,293 in England. Snow's views were that there was a specific poison present in the excreta of patients which set up the disease when particles were ingested by others ; that these particles multiplied in the second patient who similarly conveyed the infection to others, perhaps many if the " poison gained entrance to a drinking water supply." Budd of Bristol suggested that there might be a special living organism, fungal in nature, which multiplied in the intestine and gave rise to the symptoms, and was disseminated in food and water, and consequently prevention would be attained by disinfection of the evacuations of the patient and safeguarding the water-supply. At the same time Drs. Baily and Gull reported to the Royal College of Physicians that spread of cholera was independent of contact between sick and healthy and that in their opinion infection was probably wind-borne.

We are now in a position to sum up the views held in the

middle of the nineteenth century and the following decade (1850–60) as to the causes and mode of propagation of cholera; they were an attempt to effect a compromise between the two directly opposite opinions as to its contagiousness or non-contagiousness, and the outlook of the day was pessimistic. These views may be brought together under the following twelve propositions, based on Ranald Martin's observations.

1. Cholera is produced by a special poison of eastern or foreign origin, certain local conditions, and predisposition in the inhabitants being necessary.

2. Diarrhœa, dysentery and other forms of flux precede the true epidemic and prepare the people for its inception. [These might be early cases not very severe, or, as in the case of the Broad Street Pump outbreak in Westminster in 1854, a non-specific enteritis might be prevailing, true cholera developing when by some chance the vibrio enters upon the scene.]

3. After subsidence of an epidemic, mortality from fluxes never entirely recedes within its former limits. [That is, residual cases would be seen and possibly carriers.]

4. People at home were more ready for attack by disease of a flux character, perhaps owing to extension of the great town system. [That is, there would be more crowding and bad sanitation.]

5. Thus, it might be smouldering in England but the flame causing conflagration might be brought from the East; "the local insalubrity amidst and around us requires the combined influence of a certain atmospheric condition to produce the pestilence." The 'terrene' and 'the atmosphere' are inert when apart, but when they meet they become the 'shears of Fate' and true cholera results.

6. Meteorological conditions such as favour chemical decomposition of organic substances and so lead to contamination of the air, assist the spread of cholera; thus high barometer, low temperature (60° F.), small rainfall, still air and overcast sky. [But, that this was rather of the arm-chair type of argument was indicated by the observation that under similar atmospheric conditions some localities would escape while neighbouring localities were suffering severely; even neighbouring streets might be attacked while others remained free. Further, in places abroad, meteorologically all the conditions spoken of as suitable might be present and an outbreak be expected, yet none would occur.]

7. The disease would show a tendency to linger in certain districts, or, after attacking a place at the beginning of its visi-

tation, it might again return before its close, after an interval during which the district might be free of it. Or, later outbreaks might start from the same place, an "additional proof that local circumstances have great influence in determining its seat." [Carriers were unheard of in those days, though, as we shall see later, the carrier question of cholera does not rest on such firm ground as the typhoid carrier.] Thus, Acland noted, when writing of cholera in Oxford, that "those yards and streets in St. Thomas's parish, with one exception, which had been attacked with cholera in 1832 and 1849, were visited by the disease in 1854."

8. Local causes of insalubrity were universally considered necessary to the evolution of an epidemic, by producing a low state of general health.

9. Dr. Carpenter's zymotic theory was coming to the fore, that the special poisons of smallpox, scarlatina, typhus, cholera and so on were capable of exciting each its peculiar fermentation in the blood "already charged with organic compounds in a state of retrogressive change."

10. The "exciting cause was more likely to be simply toxical, because new arrivals from a pure atmosphere and in sound health are often prone to suffer after a brief exposure to the epidemic influence before any predisposing condition of the blood could be set up."

11. Pettenkofer's view was that the nidus was not in the air or water, but in the soil itself. The subsoil, if damp and porous, was readily penetrable by decomposition products of human and animal excrement. In such a soil and in the presence of this peculiar organic matter the cholera poison is generated. The ferment setting up the decomposition of which the cholera poison is one of the products is the matter of the dejecta of cholera patients. The germ-bearing excrement becomes finely divided and cholera miasma is produced.

12. Farr, Acland, Sutherland, and Snow favoured the idea of impurity of water, though they seemed to feel that impure water alone would not constitute a necessary factor of cholera, nor would mere odour, 'privy odour' as it was termed.

To recapitulate, we may say that cholera was probably not known in Europe before the nineteenth century; three times it spread from India to Russia and Europe overland, once by Mecca pilgrims to Egypt (see later), and thence to Marseilles, whence in 1865 a woman introduced the disease into Paris. The outbreaks of 1865, 1873 and 1884 came to France by way of the Mediter-

ranean, and in the last the route was traced from Alexandria to Naples, Marseilles, Toulon, Nantes, Paris and Spain and in the following year reappeared in Toulon. Before we speak of more recent outbreaks we must tell of measures taken to cope with the disease by certain Commissions appointed from time to time to consider the question and give advice.

In 1866 a Conference was held at Constantinople but did not accomplish very much beyond stabilizing, as it were, the information already acquired. The members found that India was the permanent home of cholera, that the disease was propagated by man with the rapidity of his own movements, that water and food might serve as vehicles, and that the most potent of all causes was the movements of pilgrims who tended to develop and propagate it. There was no evidence that animals could spread infection, at the same time it was only rational to regard them in certain conditions as under suspicion. The Conference supported the conclusions of Baily and Gull (v.s.) and recommended measures of general cleanliness, fresh air, avoidance of over-crowding, disinfection of buildings where cases occurred on shore, and of merchandize or ships if cases occurred on board. .

The reasons why more was not accomplished at this Conference were probably the differences of opinion at that time as regards the mode of infection, and in consequence the difference in quarantime measures proposed by different countries, arbitrarily made and independently carried out, which resulted in sudden interruption or stoppage of traffic, not only personal but also commercial.

A second International Sanitary Conference was held in Vienna in 1874 to draw up quarantine regulations which would be generally acceptable. The subject of cholera was debated under four heads : First, its origin, nature and infectious character ; second, quarantine matters proper ; third, the establishment of stations for the study of cholera, whether these should be temporary or permanent, where they should be placed, whether there should be an International Central Committee to consider the results of investigation, and, if so, whether this should be temporary or permanent ; fourth, whether the quarantine rules should be such as would militate against cholera only or against other epidemic diseases also. The conclusions as to quarantine are too important to be cursorily mentioned and will be dealt with later when we consider historically the part played by quarantine measures in prophylaxis ; as regards the other points considered, the conclusions reached were that Asiatic cholera spontaneously developed in India [*i.e.* was

its home, or endemic centre], and that' it was not endemic except
in India ; that it can be transmitted by man coming from a place
where the germ already exists and that transmission may be by
the personal effects, as soiled linen, or be carried in these effects
if they are shut away to prevent free contact with air. Further,
the infection may be propagated [transmitted ?] by drink, espe-
cially by water, and by merchandise under certain conditions.
The following general preventive measures were recommended :
Inspection of ships from infected ports, detention of infected
persons, disinfection of the clothes and effects of the patients and
passengers and of the cargo after the sick have been removed
to hospital.

In 1875, a year after the Vienna Conference, another was held
at Brussels to consider the Prevention of Cholera. The outcome
of the deliberations was that the " cholerigenic miasma spontane-
ously developed in certain conditions " in India, notably in the
Delta of the Ganges and the low-lying districts surrounding Madras
and Bombay, and had migrated thence to Europe, Africa and
America ; that cholera was contagious and its poison could be
dissolved in water and diffused in air. Limited outbreaks have
occurred in Europe, it was acknowledged, and it was a question
whether these were due to the spontaneous production of the
cholerigenic miasma in European soil or to the slow development
of miasma left by the preceding Asian epidemic. [Such verbose
tautology is not very helpful.] They were on surer ground in
concluding that the sources of contagion were the ejecta, the
corpse, the linen and clothes, ships, rooms, carriages, latrines,
contaminated water, the air (but at short distance only), animals
and merchandise—no great advance on the records and opinions
of Dr. Snow in the eighteen-fifties. This miasma, they averred,
penetrated by way of the pulmonary and digestive passages.

Ten years later a Sanitary Conference was held at Rome and
recommended disinfection to guard against the introduction and
spread of cholera, referring more particularly to vessels, their
reception and treatment at ports of arrival. Meanwhile, in 1883,
the Local Government Board issued a circular to local sanitary
authorities, enclosing copies of a memorandum on the precautions
to be adopted in view of the suspected approach of cholera and
stating that the trouble and the cost incurred would not in any
event be wasted, since those conditions which favoured the spread
of cholera favour that of other diseases also and that sanitary
improvements which would confer security against the appre-
hended importation of cholera would, even if the invasion by

cholera should not occur, be amply justified in the prevention of other epidemic diseases.

In November 1869, the Suez Canal was opened and, as Professor Greenwood writes in his *Epidemic and Crowd Diseases,*

it was naturally expected that the dangers of an extension of cholera would be thereby intensified. In 1870 only 26,758 passengers passed on shipboard through the Canal, but by the end of the nineteenth century the number had increased almost tenfold (252,694 in 1905). Actually, however, no case of cholera was seen in Europe or Egypt for eight years.

Again

The relapse into barbarism of 1914 might have been expected to favour the diffusion of cholera, and, indeed, a considerable prevalence occurred in the eastern and south-eastern parts of Europe. Germany, Austria, Italy, all acquired cholera, ultimately from Russia, but, on the whole, cholera hardly assumed the importance which its past history entitled us to expect. Since the war, cholera has, as an epidemic phenomenon, been confined to Asia.

Nearly half a million cases occurred in India in 1921 and some 300,000 in 1924, but Europe was not invaded.

During the Great War, in fact, cases of cholera were remarkably few. There was a mild outbreak at Krenes on the Danube and twenty-five cases at Cracow in 1914 (Rogers), some in North Bosnia and a few at Kiel in 1915 ; in 1916 there were a few cases among Russian prisoners in a German camp and in the following year 109 among German troops in Turkey and Palestine. In the last year of the War cases were reported in Russia, Poland and West Prussia and eighteen in Berlin—no epidemic fortunately in Europe during the period of stress.

Much more might be written concerning cholera in Europe, but the above sketch must suffice and we must now turn again to the East.

China has been the scene of many outbreaks since the disease was introduced into that country from India in 1817. Whether the disease Huo luan (sudden disturbance), an abdominal affection, was true cholera or not cannot now be determined with certainty, nor whether this was an endemic infection, but within historical times all the early outbreaks arose from imported cases, either by land as in 1817, or by sea as in 1820 (see below). Since then, records more or less reliable have been kept and between 1820 and 1937 there have been nearly fifty invasions of greater or less severity, and, thanks largely to the researches of the staff of the

Chinese National Quarantine Service, the most important have been noted. Shanghai has been attacked again and again. The town stands on an alluvial flat, ten miles from a branch of the Yangtse River. The country is divided up by creeks and artificial waterways serving the twofold purpose of transport and irrigation. The ground water is high, rarely as much as two feet below the surface, and is affected by the tides. In 1889 the city contained about 200,000 inhabitants and the Foreign Settlement 4000. Less than half a century later, in 1934, the population of the city, with Chapei and Nantao, was 1,902,762, or nearly ten times as great, of whom the Chinese comprised 1,892,288 and foreigners 10,474. In addition the International Settlement had a population of 1,148,821, of whom 1,100,496 were Chinese and 48,325 were foreigners, and the French Concession a population of 498,193, Chinese 479,294 and foreigners 18,899, giving a grand total for Shanghai of over 3½ millions (3,550,376). As long ago as 1889 it was noted that cholera made its appearance in the town every summer—rarely before the end of July, being well established in August, reaching its peak in September, dying down in October and disappearing at the end of November. The climate in June is hot and the humidity is high ; in July and August hot but dry, in September hot, damp and sultry, and thereafter cooler. In short, there is tropical heat for two months or so before the disease takes on epidemicity ; the conditions, as regards position and climate, are strongly reminiscent of those of the Ganges and Nile deltas. The custom of utilizing excreta for fertilization of market gardens is conducive to the spread of fæcal-borne infection—cholera, enterica, dysentery. The following is a list of the chief outbreaks in China ; the information has been obtained largely from the records of Dr. Wu Lien Teh and his colleagues of the Quarantine Service.

1817 First invasion of China by cholera by land route from India.
1820 First invasion by sea route from Burma and Bangkok, reaching Canton, then Wenchow, Ningpo and the Yangtse Valley. The outbreak continued into the following year when it reached Peking and the Shantung Province.
1822–4 Outbreaks in Peking, Central and Northern China and Chinese Tartary.
1826 Reached Peking from India, then crossed the Chinese wall and swept through Mongolia to Moscow.
1840 Cholera imported from India by the European and native troops ; it invaded Peking and passed along the caravan routes to Russia.
1841 Outbreak at Ningpo.
1843 Outbreak at Amoy.

1848 Outbreak of considerable severity in Shanghai.

1851 At Ningpo again.

1856–8 Outbreak at Macao.

1862 Widespread epidemic invading Peking and later Newchong and Japan. Thousands are said to have died of it in Shanghai.

1864 Epidemics at Foochow, Shanghai and Ichang.

1877. The same places invaded as in the 1864 epidemic. In Shanghai there were many cases and twenty-two deaths among the foreigners. Ningpo, Tientsin and Newchang also attacked.

1881 Outbreaks in Hainan, Canton, Foochow, Shanghai, Yangchow, Nanking, Wuhu and Seoul.

1882 Again in Hainan and Yangchow; also Wenchow, Shanghai (where 109 Chinese and fifteen foreigners died of it), Soochow and Amoy (where quarantine regulations were introduced).

1883 Widespread epidemic extending from Canton to Manchuria, and from Shanghai to Hsuchow. In Shanghai there were 251 Chinese deaths and twenty-three among the foreigners.

1885 Outbreak in Foochow, Wuhu, Ichang and Shanghai. In the last there were 522 Chinese and twenty-five foreigners died.

1887 Outbreaks in Lienchow, near Pakhoi, and Ningpo, Shanghai (where 375 deaths took place), Chinkiang and Chefoo.

1888 Many localities invaded; the epidemic extended from Kwangtung Province to Shantung and Korea. In Shanghai 282 Chinese and five foreigners died.

1890 Shanghai again suffered severely and 605 deaths occurred from it there; other places attacked were Ningpo, Wuhu, Tientsin and Korea.

1891 Swatow and district; also Korea and Shanghai again where 231 died.

1895 Widespread outbreak affecting Pakhoi, Swatow, Wenchow, Soochow, Chinkiang, Hankow, Shanghai and other places. In Shanghai deaths numbered 925.

1898 Severe outbreak in Amoy.

1902 Many parts of China and Manchuria reported outbreaks. In Shanghai alone 1500 deaths occurred.

1903 Lungchow, Amoy and Shanghai (193 deaths).

1906 In Shanghai 193 Chinese and four foreigners died.

1907 More severe again in Shanghai where 655 deaths occurred; other districts attacked were Pakhoi, Wenchow, Ningpo, Tientsin, Tangshan and Chefoo.

1910 Lungchow, Swatow, Chinkiang, Hankow, Ichang, and spreading on to Dairen.

1912 Hainan, Hong Kong, Amoy, Swatow, Shanghai (1307 deaths). Nanking, Hangkow and Changsha.

1914 Wuchow and Shanghai (350 deaths); also Hong Kong, Canton, Nanking, Hangkow and elsewhere.

1919 Many provinces invaded. In the International Settlement in Shanghai 648 deaths took place. The outbreak extended from Foochow to Harbin and is said to have caused 300,000 deaths.

Though Shanghai may be a distributing centre there is no evidence that cholera is endemic there. As regards Northern

China and Manchuria the infection is always imported, but it may spread rapidly as in this epidemic. The first case was at Newchang, a port of Manchuria, on 22nd July; the disease reached Harbin by 5th August and in six weeks there were 13,000 cases in Harbin with 4,500 deaths.

1921   Yochow, Nanking, Shanghai and elsewhere. In the International Settlement 119 deaths occurred.

1923   Seven hundred cases reported in Shanghai.

1925   Swatow, Shanghai (467 cases), Soochow, Changchow, Nanking and Yunnanfu attacked.

1926   Widespread epidemic invading many parts of China and passing on to Manchuria. Shanghai reported 366 deaths.

1929   Hingwha, Shanghai and several coastal towns of South China invaded. Severe in Shanghai where 3513 Chinese cases were notified and 347 died; forty-two foreign cases of whom six died.

1931   Outbreak in Shanghai but not of the usual severity; 482 cases were reported and fifty-seven deaths—a case mortality of 11·8 per cent. An anti-cholera campaign was undertaken in the town and 700,000 were inoculated.

1932   A widespread epidemic involving Shanghai, Kashing, Ningpo, Nanking, Wuhu and other Yangtse ports; also Canton, Swatow, Amoy, Tientsin, Peking, Dairen, Newchang, Shansi and interior provinces, Shensi, Hunan, etc., fully 100,000 cases in all. In the Shanghai area there were 4281 notified and 318 deaths. The fatality rate was, therefore, 7·4 per cent., a marked reduction on that of the previous year. It would appear that the vaccination had done some good. In Peiping the fatality was appalling, 391 dying among 493 notified, or 79·3 per cent.

1937   Severe outbreak reported from Hong Kong, between June and September. It was almost confined to the Chinese and to the more destitute of them; streams of refugees were fleeing from the parts invaded by Japan, but most of them had received inoculations. The peak was reached in the week ending 22nd August when there were 314 admissions to hospital and 205 deaths.

In Canton there were between 3000 and 5000 cases from 15th July to 1st September with a fatality of about two-thirds. In Shanghai the cases rose in number to 394 in the week ending 11th September, but deaths were only thirty-five, or 8·9 per cent. Infection spread rapidly along the Yangtse Valley. As usual the numbers began to fall in September, though this was not looked for as confidently as in previous years because of the dangers associated with movements of troops and refugees. Vaccination was carried out in Hong Kong and Canton, 'filtering stations' being set up along the Hangkow–Canton railway.

The disease was present also in other parts of Asia; thus, in India, including Burma, 3628 cases were notified in the last week of July.

In order to give a fairly complete list of the epidemics in China we have overstepped the more strictly chronological sequence and must now retrace our steps a little.

At the beginning of the present century, in 1902–03, there was epidemic prevalence of cholera in towns of northern India, in the Philippines, in Northern China (see above) and in Palestine. It was present also in Turkey and among the pilgrims to Mecca, Medina and the Hejaz. In 1902 it was raging in Upper Egypt and spread rapidly there and in Lower Egypt; at one time 1500 deaths were occurring daily. Flies were a pest but, according to Ruffer and Zachariades, were not believed to be playing any part in spreading infection. Measures of prophylaxis included examination of the pilgrims, disinfection of the clothing of patients, replacement of the water-skins by tin cans, separation of suspects, and so forth.

In the report of the Vienna Conference already referred to some interesting figures are given as to the part played by cholera in the mortality figures among British troops in India. Unfortunately actual numbers attacked are not shown, but the deaths per mille from cholera and the same from all causes are shown for Bengal, Madras and Bombay for the period 1858–71, as seen in the following table taken from the Vienna Report.

Year.	Bengal.		Madras.		Bombay.	
	Deaths from		Deaths from		Deaths from	
	Cholera.	All causes.	Cholera.	All causes.	Cholera.	All causes.
	Per mille.	Per mille.	Per mille.	Per mille.	Per mille.	Per mille.
1858	9·16	111·07	—	—	—	—
1859	8·67	45·35	—	—	—	—
1860	12·04	36·77	—	21·14	—	31·70
1861	23·73	45·93	—	16·30	—	24·72
1862	9·61	28·11	—	18·16	—	24·60
1863	4·09	24·12	—	19·51	—	16·14
1864	2·55	21·10	—	20·10	—	15·90
1865	3·12	24·24	—	22·40	16·00	35·50
1866	1·37	20·11	2·30	21·70	0·60	12·70
1867	13·84	30·95	0·36	18·00	5·00	19·30
1868	1·81	20·11	0·50	19·30	0·80	13·90
1869	16·46	42·89	2·20	23·30	5·20	21·40
1870	0·63	21·90	3·50	19·20	0·10	16·70
1871	0·71	17·83	3·32	20·10	0·09	14·42

For 1872 the number of cases of cholera per mille is also given, from which will be seen how very high were the fatality rates; all the figures are per thousand.

	Death Rate, all causes.	Cases of Cholera.	Deaths from Cholera.
Bengal	27·36	17·60	11·90
Madras	18·89	0·30	0·10
Bombay	18·86	4·50	3·70
Rest of India	24·14	11·60	7·90

Coming to more recent times ; the population of British India in 1921 was 318,942,000 and between 1923 and 1934 deaths from cholera totalled 2,490,409, an average of 207,533 per annum. In the Punjab between 1924 and 1929 only a small proportion of the outbreaks were of the explosive type due to contaminated water ; the more slowly spreading outbreaks are associated rather with bad conservancy and are probably fly-borne. [Experimentally, bred flies showed infection of the gut five days after feeding on cholera-infected food.]

Van Hunsell, in an article of much interest published in 1936 in *Geneesk. Bladen uit Klin. en Lab. voor de Praktijk*, compares British India with Java and Madoera whose population is a little more than one-tenth that of British India. In 1920 the population was 34,984,171 and in the two years 1927 and 1928 deaths from cholera were sixteen and one respectively.

An instructive map shows the infection of important parts of British India, Siam, French Indo-China, China and the Philippines, and the freedom of the Netherlands Indies, Australia and New Zealand.

2. Pilgrimages and the Spread of Cholera

The most superficial study of cholera outbreaks will convince anyone of the important part played by pilgrims and pilgrimages in their spread, and some of the classical historic epidemics have arisen therefrom. One of the earliest of which we have any reliable record is the pilgrimage in Bengal in 1783 which, however, did not, so far as we have been able to ascertain, result in a spreading epidemic, but remained confined although the number of victims was great. Twenty thousand are said to have died of the disease, but fortunately its influence was confined to the bathing-places and ceased when the multitude dispersed, differing thus from those of Hardwar in 1867 and the Ganges in 1891.

Since the beginning of the nineteenth century the endemic area from which epidemics have started has been Lower Bengal and the means of spread human intercourse, and the chief of these means the pilgrims. These pilgrims number some 20,000,000 yearly and one fruitful source of infection is the Hardwar Fair which is held every twelfth year.

Johnson in his work on *Tropical Climates*, published in 1813, notes the condition of affairs at pilgrimage season on the Ganges from which we see how they would favour the origin and spread of an outbreak.

The banks of this river present, particularly about the rising and setting of the sun, a motley group of all classes, and sometimes both sexes, sacrificing to the Goddess Cloacina, in colloquial association, not, indeed, offering their gifts in temples, but committing them freely to the passing current.

A few details of the 1867 outbreak which originated there will be of interest. The Fair is held on the banks of the Ganges and the river runs through the camping-ground which has a length of nine miles and a breadth of three miles and a surface area of twenty-two square miles, on which are camped some 3,000,000 pilgrims. Arrangements are made to accommodate them ; thus, from the conservancy point of view dry earth is adopted every-where, all filth has to be got rid of rapidly by burying or burning, screened latrines are installed in convenient situations, and no latrine or trench is permitted on ground where the contents would be discharged into a watercourse.

At the pilgrimage in 1867 the pilgrims began to arrive on the 1st April and were settled in blocks laid out for their reception, and two days later the Fair began. On the 9th there was one case of cholera. Two days later there was a heavy thunderstorm and rain continued all that night and the next day. The pilgrims were drenched and chilled and excrementitious matter was washed from the latrines and the surface soil into the river. Noon on the 12th was the ' bathing hour,' the bathing-place being a space of 650 by 30 feet railed off from the rest of the river. Into this relatively small area the pilgrims crowded as closely as possible from early morn till sunset, the rain pouring down all the time. The water soon became thick and dirty from washing of the bodies and the clothes of the pilgrims and from the ashes of the dead brought by relatives to be deposited in the water of their river god. The regular procedure, in fact the strict ritual, was for the pilgrims on entering the stream to dip under water three times or more and then, while praying, to drink of the holy water.

Next day, the 13th, there were eight cases of cholera, and two days later the pilgrims dispersed, some in bullock-drawn conveyances covering fifteen to twenty miles a day, others on foot. They carried the infection with them, the roads becoming lined with victims; many bodies were cast into the canals and the adjacent fields were studded with the flames of funeral pyres. Others in passing through communicated the disease to the villages and towns and thence by four main routes over the whole of Hindustan: West by Bajwanpore to Multan; north-west by Roorkee to Hissar and Jeypore; south by Meerut to Allahabad, and south-east by Nujerbad and Bijnaur towards Oudh. It is quite a simple matter to trace the route of spread. South to Aligarh on 20th April; on the 24th it reached Shahjahanour and passed on to Oudh; to the north-west reaching Peshawar on the 11th May and passing on to Cabul and attacking the European cantonments; from Peshawar it crossed the frontier into Kashmir and Afghanistan in July, August and September. Eight thousand died in a month in Cabul.

After an uneventful interval of many years cholera again appeared in 1891 among the pilgrims gathered in the Ganges delta, but before the gathering reached a large number they were dispersed and carried the infection over the Punjab into Kashmir and Cabul, whence it spread to Persia and Samarcand, to the Caspian and thence on to Astrakhan and cities along the banks of the Volga to the centre of Russia, and in the south to Shusha near the Turkish border and on to Tiflis. Nearly a million died of the disease in Russia. In this epidemic the infection spread in Europe to reach Hamburg and this is important on account of the studies carried to a successful issue there concerning transmission. Hamburg was supplied with unfiltered water from the Elbe, and Russian immigrants washed their clothes in the river. The population of Hamburg was 600,000, and among them were 17,000 cases with a 50 per cent. fatality, 8605 deaths occurring. Altona was lower than Hamburg and the water supplied to it was contaminated with Hamburg sewage, but their water was subjected to a slow sand filtration; among a population of 140,000 there were only 328 deaths. Had the proportion relative to the population been the same, the last would have been 2008, so that although the water, before filtration, was even worse than that supplied to Hamburg the number of deaths from cholera was relatively less than one-sixth that of the latter. One small group of Hamburg houses, with 345 inhabitants, was supplied with Altona water and among them were no cases. Since Hamburg and Altona formed

practically a single city, merely a street separating them, the few Altona cases might be due, not to the water, but to personal contact and food and fly-borne infection.

One more example will suffice. In the summer and autumn of 1902 there was a serious outbreak of cholera in Egypt; in successive weeks the numbers of notifications were 1127, 2040, 3875, 7758, 9466 and 6388, after which there was a rapid drop. The infection was traced to pollution of a well water by pilgrims returning from Mecca. One was seized with symptoms of cholera at Tor, on the Gulf of Suez. Returned pilgrims frequented the mosque in the centre of the village at Moucha, and the latrines were situated close to the village well. The earliest patients took water from this well. Between August and 1st October 35,000 cases were officially reported in Egypt. The disease spread into Syria. On the 8th October an outbreak was reported from Gaza and from Lydda, near Jaffa.

Dr. R. B. Lal has summed up the question of the dangers of fairs and festivals in India in a recent article (*Indian Med. Gaz.* 1937). He shows that there are two kinds of pilgrim centres : places of perennial pilgrimage of special sanctity, and temporary camps for periodical fairs and festivals, to which come millions of devotees from all parts of the country, ignorant, poor many of them, and undernourished, exposed to the vagaries of the weather with little protection. Important among the periodical festivals are the kumbh fairs held every twelve years at Allahabad, and the Adha-kumbh Fairs held six years after the former. In the past these fairs have played an important *rôle* in the epidemiology of many diseases, but particularly of cholera. Now, much more effective precautions are taken. Directors of Public Health of different Provinces and the Medical Officers of railways draw the attention of pilgrims to the risks they run and inoculate them with vaccine. The pilgrims are inspected *en route* at important stations and finally at Allahabad. Any sick are removed to hospital. District boards are responsible for sanitary arrangements for those travelling by road—the camping-grounds, wells, tanks and so forth.

The Fair, held in a triangle of ground at the confluence of the Jumna and the Ganges, lasts a month. At the 1936 Fair there were about 50,000 temporary residents, and bathers on the most important day of the festival numbered one and a half millions. Deep trench latrines were installed, rubbish removed to pits and burned. Drinking water was supplied from two deep tube-wells with an overhead reservoir yielding 2500 gallons an hour, and

standpipes were plentiful. There were two temporary hospitals erected, one for general and one for infective patients, also forty-two small branch hospitals and four dispensaries. Roads were watered to keep down dust, cleanliness reduced the fly menace to a minimum. Lectures, exhibitions and films assisted health propaganda. The success of the measures taken was evidenced by the fact that throughout the fair there were only three cases of cholera.

3. CAUSATION

Dr. John Macpherson, Inspector-General of Hospitals of the Bengal Army, discussing the first pandemic of 1817 and its causation deals in turn with contagion, direct or indirect, with Bryden's theory of air propagation, with propagation by the agency of water and of the soil and with the parts played by season and weather. We need not take up time and space by considering his views on all of these, but it is of interest to note his ideas on three of them. Propagation by *water* he dismisses very briefly with these words : " The school that believes in the propagation of cholera mainly by water polluted with its germs is essentially English." [Macpherson was a Scotsman.] Under the heading of *soil* he mentions Pettenkofer's ideas and adds : " In his views, as he now expresses them, it appears to me that the presence of the dejections of cholera occupies a less prominent place than formerly." *Season* and *weather* " undoubtedly influence the propagation of cholera. In one sense they may be considered as the aggregate results produced by . . . air, water and soil—as influenced by light, heat and electricity." For one who had had so much practical experience of cholera and held so high a position in the medical world of India this is not a very enlightening explanation.

James Kennedy, in his *History of Contagious Cholera* published in 1832, states what he calls the five " Laws of Cholera." These are :

1. *Climatic influence.*—The contagion of cholera may spread in every climate, with its spreading powers but slightly or not at all impaired.

2. *Predisposition.*—Persons in certain states of bodily health are peculiarly liable to be attacked, as the fatigued and under-nourished.

3. *Latent infection.*—The period of time during which the contagion lies dormant in the system rarely exceeds three days. [By this he seems to mean the incubation period.]

4. *Increase* and *Decline.*—When the cholera appears in a town it extends rapidly, and, in general, runs its course in the space of a few weeks.

5. *Contagion.*—Cholera is contagious and its contagion is of a highly diffusible nature.

In view of this mention may be made here of a Medical Committee at Moscow (reported by Bisset Hawkins) which took up the peculiar position that goods and effects could not communicate the infection of cholera because " convalescents have continued to wear the clothes which they wore during the disease, even furs, without their having been purified and they have never had a relapse.

The knowledge of cholera being water-borne is shown in the following extract of the nineteenth century ; the exact year and source we have not been able to trace.

> So born and fed 'mid Tauran's mountain snows,
> Pure as his source awhile young Ganges flows ;
> Through flow'ry meads his list'ring way pursues,
> And quaffs with gentle lip the nectar'd dews ;
> Then, broad and rough, through wilds unknown to-day,
> Through woods and swamps, where tigers prowl for prey,
> He foams along, and rushing to the main,
> Drinks deep pollution from each tainted plain.

The ' theory,' much debated in the middle of the nineteenth century, that drinking water might be the means of conveying the ' cholera poison ' had its ardent advocates and its equally ardent opponents. Each side put forward its view in a very partisan manner, leaving to those addressed the choice of accepting *either* the soil theory *or* the drinking-water theory, disregarding entirely the possibility that the two might be combined as by soil infection gaining access to drinking water, such as wells, or again that there might be a mode of acquirement differing from both of these, as from food contaminated by soiled hands, flies, etc. The investigations of Dr. Snow into the Broad Street pump water and its relation to the cholera outbreak in Westminster in 1854 (see *Some Notable Epidemics*, 1934) sufficiently demonstrated the former—the fouling of drinking water by dejecta preparing the way by causing diarrhœa before the actual *specific* infection by cholera came about.

Those who studied the question in those days had no doubt as to the communicability of cholera, though not necessarily direct since it was observed that attendants on the sick might and often did escape, and it was assumed that either the cholera patient eliminated some infective substance which in its primary form had no potency as a cholera poison and only attained its specific power and properties after it had undergone some change or maturation outside the body, or that the multiplication or reproduction of the cholera poison proceeded independently, as it were,

of the patient, and clung to the person, whether healthy or sick, or to other objects, being carried by them from place to place and giving rise to an outbreak more widespread, even epidemic, when it met with conditions suitable to its reproduction.

That flies might be the agents of spreading infection was believed long before the organism was discovered by Koch in 1882. Nicholas writing to the *Lancet* in 1873 notes that when in 1849 cholera prevailed at Malta,

My first impression of the possibility of the transfer of the disease by flies was derived from observation of the manner in which these voracious creatures, present in great numbers and having equal access to the dejections and food of the patients, gorged themselves indiscriminately and then disgorged themselves on the food and drinking utensils.

Flügge (*Die Mikro-organismen*, 1886) draws attention to the fact that the worst months for cholera are those in which insects abound and, in 1893, from the experiments of Uffelmann and others to the danger of this particularly in small households where there is no adequate separation between cholera patient and the kitchen or larder.

Meanwhile Celli had reported (in 1886) that organisms, notably *Bacillus anthracis*, *Bacterium typhosum*, *Vibrio choleræ* and *Staphylococcus aureus*, were still virulent after passage through the fly's alimentary canal.

The part played by soil was for long undoubted, and workers in India were confirmed in that opinion by observing that the hill men, while in their native surroundings, did not suffer, but that if they came down to the plains they were no longer exempt, but were attacked as readily as the local plain dwellers. Doubt was, however, strengthened by the evidence of epidemic outbreaks on board ship, showing that the ' soil theory ' did not fit all cases, although it was widely believed that the best way to avoid infection was to put out to sea ; nevertheless, the fact that epidemics did occur on board from time to time showed that there was no real immunity at sea. At the same time ship outbreaks were not very common and there were reasons to suppose that such outbreaks when they did occur could be referred to infection acquired while the vessel was in port and thereafter other members of the crew might be attacked in series.

In short, ship outbreaks resembled house outbreaks and were often confined, for a time at least, to one particular deck or section of the vessel, and especially to those least favourably situated,

as the steerage or 'tween-deck passengers. Diffusion, in short, was noticed to follow human intercourse, by dejecta, clothes, contact, as exemplified by military campaigns, pilgrimages and such-like. Failure to discover the route of importation and the track of spread arose from the difficulty of watching and controlling traffic, especially the transit of goods, as often as, perhaps more often than, conveyance through direct personal intercourse.

In Macnamara's day (1876) the 'seven characteristic features of cholera' were :

1. *Its unequal and very partial distribution*—he instances among others the fact that in 1817 the prisoners of Alipon gaol were free from the disease which was raging outside the prison walls.

2. *The inhabitants of certain localities are especially liable to be visited by cholera*, these localities having features in common which differ from those of places which are not attacked. He notes in this connection the greater prevalence and fatality in large seaport towns built on low-lying alluvial soils, at river mouths, and often thickly populated.

3. No amount of overcrowding, no special condition of soil will cause cholera to arise *de novo* among men removed from its endemic influence. Thus, it would be absent from Mauritius and the West Indian islands, for example, until the arrival of vessels with cholera cases on board or a history of such.

4. Its intensity varies, having periods of less and more activity and well-marked periods of increase, culmination and decline.

5. After an outbreak it disappears entirely from a locality for a time, except of course in endemic centres. Thus it invades and disappears from Europe and America, but remains endemic in Bengal and Java.

6. All epidemics can be traced back to Hindustan through a continuous chain of human beings suffering from the disease or through articles soiled with their dejecta.

7. Lastly, the more explicit the examination the clearer does it appear that, in the majority of cases, the disease spreads from one person to another by means of cholera fomes finding its way into the drinking water and thus into the intestines of other people, as exemplified by Dr. Snow's work in Westminster already referred to, by that of Dr. Richardson on the spread of infection in the Navy in the Crimea in 1854, and by Dr. Farr's account of the Newcastle outbreak of the same year.

It will be seen that these 'characteristics' are common to many infective diseases and are not 'characteristic' in the sense of being 'peculiar to cholera.'

Later ideas, until we come to the discovery of the causative organisms, are merely amplifications of the foregoing with one exception, the part played by climate and, in particular, humidity

in the epidemiology of cholera, as elaborated by Sir Leonard Rogers.

Sir James Ranald Martin about the middle of last century mentions six theories regarding the cause and propagation of cholera ; they are historically interesting as summing up the state of knowledge at the time and as showing how the way was being, as it were, prepared for discovery of the vibrio, by indicating an organismal cause which was not actually proved till some thirty years later.   These theories are as follows :

1. Cholera spreads by atmospheric influence or epidemic constitution and a susceptibility in the inhabitants, produced by habitual respiration of an impure atmosphere. [One could hardly call this a cause, but rather a statement of the conditions under which the disease could spread.]

2. Cholera is a contagion—a morbific matter increasing in the human body and propagated by emanation from the bodies of the sick.

3. Snow's theory—the poison is swallowed, acts on the mucous membrane of the intestines, is reproduced in the intestinal canal and passes out, much increased, with the discharges. These discharges, in various ways, but chiefly by becoming mixed with water of rivers and wells used for drinking, reach the alimentary canals of other persons and produce the disease in them. [Practically correct according to modern knowledge, if we substitute ' vibrio ' for ' poison.']

4. Cholera is due to a morbific matter or poison which, however, is reproduced only in the air, not in the body, and its diffusion is due to the atmosphere and atmospheric conditions.

5. Cholera is the result of a species of fermentation reproduced in impure, damp and stagnant air, but is carried in ships, in clothes, etc., and so diffused by human intercourse.

6. Cholera is increased and propagated in and by impure air as well as in and by the human body. This is really a combination of the second and fourth of the above.

Martin concludes by maintaining that the fermentation theory (No. 5) is the only one supported by much evidence.

The question of humidity and its *rôle* in the endemicity and propagation of cholera calls for more detail. The subject has been studied particularly by Sir Leonard Rogers. In 1926 (*Proc. Roy. Soc. Med.*) he gave an account of his investigations into the epidemiology of cholera in all parts of India, exclusive of Burma, in the preceding fifty years. The spread west from Bengal he found related to rise of absolute humidity to over 0·4 in the invaded areas in the months of the increase, while in Lower Bengal, south-east Madras and the west coast of Bombay the absolute humidity was never below 0·4 and cholera was present there at all seasons of the year. He noted also a temporary decrease in Bengal in

January and February when the absolute humidity falls nearly to the critical point, 0·4. Rogers considered and discussed the meteorological conditions in epidemic years and the close relationship for various years between deficient rainfall—that is, poor water-supply—and epidemics. The same year, A. J. H. Russell (*Indian Jl. Med. Research*) developed further what was now called the 'periodogram analysis' and showed that rainfall and temperature have little association with cholera, whereas humidity has a fairly high positive association. When rainfall and pressure effects are constant he found that temperature had a fairly significant negative correlation with cholera ; increase of pressure was associated with reduction in the incidence of cholera. When temperature effects are ignored, the association of humidity with cholera was highly significant. It is " fairly conclusive that high humidity is favourable to high incidence of cholera, while pressure is associated in exactly the opposite manner."

In a later publication (Rogers and Megaw, *Tropical Medicine*, 1930) Rogers gives the results of his investigations into the records of this disease from 1870–1930 in each district of India and shows that the outbreak of 1875–7 spread from three distinct endemic areas where cases of cholera have occurred in each of the last thirty years, namely,

a very large north-east area comprising all Assam, Bengal, Bihar and the five eastern divisions, or five-sevenths of the United Provinces ; . . . secondly, a large area comprising the central and south-east coast districts of the Madras Presidency ; and, thirdly, the narrow, hot, damp Konkan coast of Bombay.

In these—the two latter certainly—the monthly absolute humidity never falls for long below 0·4, a circumstance (see above) in his opinion favouring the persistence of cholera. From these areas pilgrims are the main introducers and propagators of infection. Sir Leonard Rogers was able to show that during a period of forty-five years there had been fewer epidemics in Lower Bengal than in the United Provinces. In practically every outbreak (forty out of forty-one) the rains of the preceding monsoon, or the winter rains, and in some cases both, had failed. Further, an unusually early rise of absolute humidity seemed to favour early recrudescence or epidemic spread of the disease, and he was able to forecast, by studying these factors, outbreaks some months ahead.

This question of cholera and absolute humidity has been even more recently studied for Shanghai, for the period of eight years to 1932, by J. W. H. Chun, Chief of the Medical Services Division,

Shanghai Quarantine Station. His conclusions as regards the Shanghai Municipalities support the theory, or view, that epidemic cholera occurs only when the absolute humidity is high, in the neighbourhood of 0·4 inch, and deficient winter and spring rainfall may be followed by a severe outbreak. Since the mean monthly temperature and the absolute humidity follow each other closely, Dr. Chun is in favour of paying attention to the former which is more readily understood rather than to the latter which is a more complex undertaking.

Bacteria as the Cause of Cholera

The idea of ' cholera animalcules ' carried by the wind from India as the endemic centre and thus giving rise to epidemics and pandemics—Ehrenberg's theory—was declared by Ehrenberg himself to be a ' piece of silliness ' after he had examined microscopically the particles in the air of cholera-stricken houses. We do not know, for Ehrenberg does not tell us, what he expected to see. Thomson also in his papers and reports on cholera between 1849 and 1856 reached a negative conclusion after " thorough chemical and microscopical investigation of the matters present in the air of cholera wards." Bryden's ' cholera wave ' theory, that endemic cholera is earthborne, but epidemics are air-borne, carried by moist winds and limited by dry winds, was also received with scepticism and finally cast aside as the baseless fabric of a vision. Certainly a spread by winds would not account for the different routes taken by the disease outside India, as over Central Asia, Europe and to America.

When the observation that extension took place along routes of travel and at the rate of travel (Bryden denied the possibility of spread by human intercourse alone) gained more and more confirmation investigation turned to the personal source, the dejecta, the blood, the intestines of patients, in the search for ' lower organisms ' which could be brought into causal connection with the disease. Pouchet in 1849 reported finding " lower organisms in the excreta of cholera patients " which he described as belonging to the species *Vibrio rugula*. We need not trace the intervening steps, for little advance was made in the next thirty years, so that in 1880 the conclusion was reached that though the parasitic nature of the cholera poison had not been proved, nor had the theory yielded fruitful results, the question could not be regarded as settled negatively, because the theory fitted better than any other the main facts known about the disease and on the other hand no known fact was against it.

We have become so used to the notion of the cholera poison multiplying within the bodies of the sick, and of the choleraic discharges in particular being the carriers of the same, that we hardly appreciate nowadays how slight a foundation there is for that opinion. A certain number of facts have been brought together from practical experience in support of it : such as the concentration of sickness in places where cholera dejecta had been deposited ; cases of illness among persons who had been employed in emptying cesspools which had received the evacuations of cholera patients ; house epidemics limited to such of the inhabitants of a quarter as had used one privy, or whose privies opened into one cesspit ; progress of the epidemic along streets in quarters of the town which had one common system of canalization. But, of all such facts, the greatest importance attaches . . . to an observation that has often been made and verified, viz. the outbreak of cholera in a locality spared hitherto, and in fact situated at a distance from the centre of a pestilence, when linen, bedding, or clothes, soiled by the dejecta of cholera patients, had been brought to it, the disease attacking just those very persons who had come into direct contact with the tainted articles.

This was written in 1881. Two years later Robert Koch discovered the ' comma bacillus ' in Egypt and confirmed the discovery in Calcutta, where he found it in the dejecta of all cases which he examined, in 1884.

N. C. Macnamara, writing in 1892, states that as far back as 1866 '' in a work published on Asiatic Cholera '' he insisted on the cause being the introduction of specific organic matter into the small intestine, that the ' vibrio ' was destroyed by the acid gastric juice, but that if the stomach was not healthy or the germs were largely diluted, they might live and develop in the small intestine and set up cholera. Macnamara does not specify the work to which he refers and there is no mention of any ' organism ' or ' vibrio ' in the index of his own larger work, *A History of Asiatic Cholera*, published in 1876. He based his opinion, he said, on experiences in Lower Bengal extending over a period of nineteen years, and it was seventeen years afterwards that Koch's discovery was made.

It is interesting to note the reception of Koch's announcement by men of repute in other countries. Both Klein and Ray Lankester declined to accept Koch's conclusions as to the specific nature of the vibrio, and Klein affirmed further that Koch must be wrong because the organism depicted was not a bacillus, but a spirillum. Koch replied, and the majority will agree that his attitude was right, '' It is all the same whether the cholera bacteria are called bacilli or spirilla, so long as one pays attention to and lays stress on their other characteristics ; the name is, in this case, of the least importance. I can, however, show

you that a capable botanist, namely De Bary, still calls curved rod-shaped bacteria bacilli."

Klein returned to the fray but does not appear to come very well out of the controversy. He stated that he found Koch's organism in the mouths of healthy men and in phthisical and dysenteric patients ; that they were to be found in quite small numbers if a post-mortem examination is carried out soon after death, in large numbers if autopsy is delayed ; further, he found the organism in tank water in India, though those living near the tank were free from cholera.

Koch rejoins : " No one knows what Klein found [we may hazard it was *Bacterium coli*] ; his report has in England been subjected to a very thorough and able criticism by Dr. Watson Cheyne. Klein was compelled in consequence to withdraw most of his assertions . . . more especially he had to admit that the cholera bacilli differed from those occurring in phthisis, in dysentery, and in the mouth ; and he had further admitted that he has found true cholera bacilli in all cases of cholera."

It is noteworthy too, as was remarked at the time, that the organisms were not found in the blood or in any of the body tissues but remained localized in the intestines.

Little further progress was made for the next twenty to twenty-five years ; on the contrary deeper study seemed rather to confuse matters and by 1907 bacteriologists were being drawn into the maelstrom of the true cholera and cholera-like vibrios. M. A. Ruffer in 1905 examined vibrios isolated from patients at El Tor, but in whom no ' cholera lesions ' were seen. A hundred and seven patients were examined and vibrios were found in thirty-eight. Six of them agglutinated with cholera serum and five, one of which was avirulent, gave a positive Pfeiffer reaction. In 1906 vibrios were found in eighteen patients diagnosed as suffering from dysentery and colitis, but presenting none of the lesions or symptoms of true cholera, although two of the strains gave all the reactions of the true cholera vibrios—agglutination, Bordet's saturation test, Pfeiffer's reaction, complement fixation and the hæmolysis test. By this last, certain vibrios suspended in saline when added to washed red corpuscles of sheep or goat hæmolyse them. No vibrio giving agglutination response, or reacting positively to the Pfeiffer and complement fixation tests gave hæmolysis ; the El Tor vibrios, however, were hæmolytic and did not fix complement and thus could be separated from the true cholera vibrio.

Controversy and research on the serological reactions of vibrios

have continued for the past thirty years and the position reached in 1936–7 is this. Recent work (1936) out in India has demonstrated that in many instances the serological reactions of vibrios isolated from secondary cases or from contacts of primary cases did not correspond altogether with those of the primary cases, although there could be little doubt the sources of infection of the contacts and secondary cases were these primary ones. These variants differed from the original serologically, biochemically and in metabolic characters. Over 300 strains were tested and if it could be shown that variations occur in the field as in the laboratory we might find an answer to the vexed question whether cholera cases arise only from previous cases and their contacts, or whether chronic carriers (see later) of certain 'chemical' groups can start an outbreak. In the following year Taylor, Pandit and Read concluded from a study of over 1000 strains that vibrios of serological type differing from true *V. choleræ* do not produce cholera, and further it seemed unlikely from their investigations that the inagglutinable strains can develop into the typical agglutinable form. More recently still, in 1937, F. M. Marras reported the results of his examination of 6124 specimens at El Tor during the pilgrimage of 1936 ; he isolated six vibrios which agglutinated with 'O' and 'O + H' cholera sera. All six were indole positive, strongly hæmolytic to sheep red cells and had been obtained from healthy persons or at least persons showing no symptoms of cholera. Marras concludes that none of the serological tests is adequate to distinguish the true cholera vibrio from the El Tor vibrio ; the somatic 'O' and the flagellar 'H' agglutinins are the same in both. Apart from the hæmolytic character of the El Tor vibrio the two types are differentiated by the fact that the El Tor organism does not produce symptoms of cholera and, he maintains, is not of epidemiological importance in cholera.

It is well known that persons who have passed through an attack of typhoid fever may continue to harbour the organism and at times to excrete it for many years—in fact, become bacteria-passers or carriers. Of great epidemiological importance is it to know whether the same holds good in cholera—are there chronic carriers of the cholera vibrio ? This question has been studied and debated for a quarter of a century and is not yet settled. It is also important to know how long soiled effects, contaminated water, and such like retain the organism. In 1909 Houston added cultures of the cholera vibrio to raw river water and found that in a fortnight all the organisms were dead and nearly all, over 99

extension through a continuous chain of human beings affected, and examination of the stools of several thousand persons in the worst cholera areas in the United Provinces did not result in the discovery of a single carrier. ' Inagglutinable ' vibrios were present in the stools of about 6 per cent. of healthy individuals, but there was no evidence to show that the carriers of inagglutinable vibrios had anything to do with the origin and spread of cholera. Dr. Saranjam Khan states dogmatically :

The reservoir of cholera is not the ' chronic carriers ' of *V. choleræ*, because they do not exist ; it is also not in the passers of the ' inagglutinable ' vibrio because they do not cause epidemic cholera. The real reservoir is in the presence in the endemic areas of patients suffering or recovering from cholera. The only sources of the infection of epidemic cholera are patients suffering from the disease in the acute stage for about four days ; also some, though to a much less extent, in the convalescing stage for about fourteen days ; and perhaps in the incubation period for a few days.

An opinion almost the direct antithesis of this is held by Tomb, Maitra, Brahmachari and others. Tomb and Maitra, using the ' open-bowl ' method of cultivating the vibrios, found that agglutinating vibrios in cholera stools, when added to village tanks, are changed into the non-agglutinating form in 24–36 hours. They showed further that as many as one-third of the inhabitants of a mining settlement in India were carrying such vibrios. The important difference between sporadic and endemic cholera is that the vibrios associated with the former are but feebly infectious and are non-agglutinating. Inconstant results were obtained from attempts to convert the non-agglutinating into the agglutinating, though the reverse is easy. Examination of the stools of convalescents in an epidemic showed that 80 per cent. of them continued to pass non-agglutinating vibrios, whereas (here they agree with Saranjam Khan) extended examination of the stools of healthy persons and survivors of epidemic cholera did not result in the discovery of a single permanent carrier of agglutinating vibrios. They conclude :

The non-agglutinating vibrio (which is itself capable of causing clinical cholera) takes on the agglutinating characteristic under certain biochemic-physical conditions in the human intestine whose nature is at present unknown, and in this mutation or epidemic form is the cause of epidemic cholera, since it is not unreasonable to assume that a characteristic so unstable may be as easily acquired as lost. Non-agglutinating intestinal vibrios, therefore, in our opinion constitute the reservoir of cholera, both epidemic and endemic.

Brahmachari, in a paper on *Non-agglutinating Vibrios, their Relation to the Typical Vibrio choleræ*, reported having examined

the stools of 2490 healthy individuals and finding 1·2 per cent. agglutinating and 12·6 per cent. non-agglutinating vibrios ; in 496 surface tanks he found 1·8 per cent. and 34·9 per cent. respectively. In July–October, when there is no cholera, no agglutinating vibrios were isolated. He further investigated the serum reactions of sixty-eight non-agglutinating strains and during a period of six months they remained non-agglutinating, after which time more than half of them became agglutinable, two of them in serum diluted to 1 in 8000 and 1 in 16,000—in short, transformation to agglutinating true cholera vibrios occurred.

Bruce White's work during the past year (1938) on the antigenic constitution of the vibrio is likely to prove valuable in facilitating diagnosis. All strains of *V. choleræ* from Indian sources were found by him to carry a particular bacteriophage, the LL cholera phage, whereas in no strains of the vibrio in cases from the· Far East was this phage found ; the El Tor vibrios also were free from it.

There we must leave the question, unfortunately still undecided. We can sum up by saying that passers of vibrios in the incubation stage of the disease are dangerous undoubtedly, convalescent carriers are probably dangerous, healthy less and perhaps not at all. There is not yet general agreement whether non-agglutinable vibrios can become pathogenic.

The subjects of vaccines and phages are postponed for the present and are dealt with in the section on treatment.

4. TREATMENT

The treatment of cholera may, for the purpose of this historical study, be considered under the following heads : (*i*) Charms and Magic ; (*ii*) Drugs ; (*iii*) Salines ; (*iv*) Phages. Quarantine and prophylactic measures are considered subsequently.

(*i*) Charms and Magic

According to Bontius (1642) *lapis porcinus* was good for cholera ; an amulet such as a circular piece of copper two and a half inches in diameter was commonly worn in Naples in contact with the skin at the pit of the stomach. A ' rarecole ' found under every root of plantine [? plantain] and, appropriately enough, under ' mugwort,' but only on Midsummer Eve was worn as a protective not only against cholera, but plague, fever, ague, and other diseases, and one man wrote that he never knew any that was in the habit of carrying this " marvellous cole " with him who ever was to his knowledge sick of the plague or complained of " any other

maladie." This ' cole ' under the mugwort seems to have been a panacea.

It was not very long ago, as recently as the 'seventies of last century, that magic was relied on as a prophylactic in a country regarded at that time as civilized, namely Russia. Wallace writes :

Cholera had been raging in the district for some time. In the village in question no case had yet occurred, but the inhabitants feared that the dreaded visitor would soon arrive and the following contrivance was adopted for warding off the danger :—At midnight, when the male population was supposed to be asleep, all the maidens met in nocturnal costume, according to a preconcerted plan, in the outskirts of the village, and formed a procession. In front marched a girl holding an ikon ; behind her came her companions, dragging a sokhâ—the primitive plough commonly used by the peasantry—by means of a long rope. In this order the procession made the circuit of the entire village, and it was confidently believed that the cholera would not be able to overstep the magical circle thus described.

(ii) General Management and the Use of Drugs

The use of drugs in this disease has been directed almost entirely to the relief of symptoms as they arose. In Stevenson Bushman's work on *Cholera and Its Cures*, published in 1850, the author gives a list of more than 150 names and the remedy suggested by each, and the reference to medical literature where it is mentioned. For details the reader must consult this work ; here we may say that the list includes electro-magnetic insulation, carbon, inhalations of oxygen, hashish (*Cannabis indica*), calomel 1–2 grains " every five or ten minutes for successive hours," cold affusions, nitric acid blisters, tobacco, wrapping in a wet sheet, " water thrown into the bladder," cupping, and lemon-juice. As Bushman expresses it, they were none of them really of use. Practitioners " gave drug after drug, draught after draught, heaping a Pelion of pills upon an Ossa of powders, in the vain hope of discovering a specific to immortalize their names."

Sir James Martin, in his work published a few years earlier (1841), remarks that

the popular theory that the discharges are an effort of nature to throw off a *materies morbi* is not only unsupported by any known facts of the disease but, when applied to practice, is found to increase the violence of the symptoms.

Calomel stands in the forefront, but is employed empirically. Martin's records, however, hardly support the claim as to its efficacy and he adds that in general no appreciable effects follow

its administration, even in large amounts given in small and frequently repeated doses. Thus, of 365 cases treated with it 178 recovered and 187 died, a fatality rate of 51·2 per cent. ; other cases reported to the Royal College of Physicians gave a return of 365 deaths among 725 cases, or 50·3 per cent. fatality.

The so-called 'rational method' was by calomel, given to restore the liver function and act as an alterative on the gastro-intestinal mucous membrane ; also opium to allay irritation and arrest discharges, and stimulants to counteract depression of the nervous system. The results of this 'rational method' were, however, no more favourable than those with calomel alone.

Another drug recommended was *perchloride of carbon* (this is not defined nor is the chemical formula given ; the time was before the days of carbon tetrachloride) given in 5–10-grain doses with camphor in chloroform. His remark on this is that it was a good stimulant but had no specific therapeutic value. *Emetics* were, he thought, serviceable if given early ; *bleeding*, unless performed very early, was in his opinion definitely bad ; nevertheless he records in his book cases of recovery after bleeding when the patient was almost *in extremis*. He mentions *salines* of low specific gravity (see later), but opium he calls the 'sheet anchor.'

Other drugs which Martin mentions as being used empirically are quinine, strychnine, arsenic, sesquichloride of iron, nitrate of silver, nitrous acid, chlorine water, sulphur, sulphuric acid, per-chloride of mercury, and charcoal, among others—an example of " a disease with many remedies has no cure." Oxygen was also tried and he gives the method of its preparation for medicinal purposes in his day. " It is easily prepared by intimately mixing potassium chlorate with one-sixth of its weight of black oxide of manganese and throwing the mixture on an iron shovel heated to dull redness."

Though Martin regarded bleeding as in general bad, others in India did not share this opinion. Often, of course, on account of general collapse and of collapse of the vein walls very little blood could be obtained, but it was thought that in cases where a good flow could be attained, thirty ounces or so being with-drawn, recovery usually followed. Clearly, for such a quantity to be obtained the case would probably not be very severe, or at least would be in an early stage. Sometimes attempts would be made to encourage the flow of blood by a hot bath but, says Kennedy (*History of Cholera*), " if a patient in acute cholera be placed, during the stage of real debility, in a warm bath, he will probably faint, and never recover from the fainting fit thus in-

duced." In a disease where the loss of fluid is already so great that the patient passes early into a state of collapse, it is difficult to see how any benefit could accrue from venesection and withdrawal of blood, especially in large amount.

The general lines of treatment in his day were, as already stated, symptomatic and consisted of administration of opium, usually as laudanum, with astringents, notably acetate of lead or diluted sulphuric acid ; the patient was allowed to suck ice *ad libitum*, which must have increased thirst, but he was not allowed to drink water or any other fluid—which seems to us a refinement of cruelty since, with so much abstraction of fluid thirst must have been intense—and a large mustard poultice was applied to the abdomen. If vomiting was severe and was not checked by the sucking of ice and the patient was becoming worse, a single dose of 20 grains of calomel would be given and, it was said, with benefit and relief. It was thought, further, that by rendering the stools acid the cholera organisms were destroyed in the intestinal canal. Friction relieved the cramps and ether was inhaled and hot-water bottles were applied for the collapse. Alcohol was regarded as harmful.

The contagious character of cholera was well known to the natives who consequently, unless called upon by duty as near relations to assist, avoided the sick as much as possible. When a village was attacked it was no unusual occurrence for the inhabitants to abandon it for a time " until the contagium was destroyed."

Little or no change was made as regards the use of drugs for the next eighteen or twenty years, till, in 1910 Rogers introduced the use of permanganates. He advised it either in solution, in a strength of $\frac{1}{2}$–1 grain of the calcium salt, increasing to six times that strength, in a pint of water, or in pills, 2 grains, with kaolin and vaselin, coated with keratin. He reported that the *fatality* rate was reduced thereby to 20–22 per cent. Eight years later (1918) Stumpf claimed that a marked reduction in mortality had resulted in Serbia by the drinking of kaolin in water or by its use as rectal lavage.

(iii) *The Use of Salines*

The employment of saline injections intravenously in the treatment of cholera dates back for more than a hundred years. Latta, of Leith, seems to have been the first practitioner in Great Britain to make the experiment in 1831, having previously made

trial of them, administering them by mouth or rectum, without obtaining any benefit. An old woman in whose case all the usual remedies had been employed in vain was given saline, six pints in all, and she made a striking improvement, but vomiting and purging returned and death took place five hours later. In subsequent cases Latta repeated the injection at the first sign of returning collapse. His formula was : Sodium chloride 120 grains, sodium bicarbonate 40 grains in 5 lb. of water at 110°–115° F., and he injected 5–6 lb. in twenty minutes ; in some cases he injected 10 lb. at a time. " Some have added a little white of egg, on the supposition that the albumen is defective in the blood ; but it has not been found useful." Dr. Christison quotes certain results and says : " No other remedy has anything like the *immediate* effect of the injection of the saline solution into the veins." It is important to note the word " immediate," for he adds that several thus brought round " died of the subsequent stage of reaction, or have fallen again into the state of collapse and, after repeatedly doing so, have at length died in that stage . . . its *immediate* effects are undoubted and most striking." Dr. Laurie of Glasgow found that all his patients so treated died in this late stage ; he thought that perhaps too large a quantity was given and he changed to 30 oz. only at a time, given slowly. Four recovered, but twenty-two died and he gave up the procedure " as not only useless but frequently hazardous."

Martin, already referred to, recommended, in 1841, giving saline of low specific gravity in place of water to restore to the blood a fluid similar to that lost in the early stages of the disease. This was, it appears, given by mouth. Injection of salines into veins gave in his view " results generally unfavourable."

The operation in all its details is a delicate one and requires not only a careful discrimination of the cases to which it is applicable, but also an exact attention to the physical characters and composition of the fluid to be injected and other collateral circumstances. Until these points receive greater elucidation, the results obtained can form no sound basis for an opinion respecting its merits.

Elucidation of the rationale of the procedure was afforded by Sir Leonard Rogers. In the middle of last century the outlook was most depressing ; according to Elliotson :

It is impossible to say anything satisfactory on the treatment of a disease which would seem every year to become a subject of greater difficulty to medicine. If all the patients [he is speaking of India] had been left alone, the mortality would have been much the same as it has been. We are not in the least more advanced as to the proper remedies than we were when the first case of cholera occurred.

Stevenson Bushman, in his book on *Cholera Cures*, devotes a whole chapter to the saline treatment, followed with much success at Coldbath-fields prison ; his figures show less than 3 per cent. fatality among 446 cases.   His remarks savour a little too strongly of special pleading and the results he gives far surpass the experience of others who had up to then tried the method.

Intravenous injection of saline was first used for cholera in Shanghai in 1875.   E. J. O'Meara was using it in India in 1908, transfusing with 0·625 per cent. saline for adult natives, but he did not consider it safe for Europeans and children [he gives no reasons for distinguishing them] and controls the progress by taking the specific gravity of the blood at the bedside, by Hammerschlag's benzene-chloroform method.   Transfusion had to be carried out slowly to bring the blood to the normal specific gravity, for if it was given quickly the fluid, he found, soon flowed from the vessels again and the diarrhœa returned.   The following year Rogers reported on the advantages of injections of hypertonic saline, 1·25 per cent., intravenously and stated that the former fatality rate was reduced to half.   He found the best guide to be the blood pressure, the aim being to get it above 100 mm. Hg. If the pulse was still fair, he gave the solution *per rectum* ; subcutaneous injection was not only too slow but entailed a risk of local abscess formation ; he sometimes gave it intraperitoneally, but if the blood pressure was below 70 mm., or if there were much restlessness with cramps and cyanosis, he employed the intravenous route, using 120 grains of sodium chloride and 3 grains of calcium chloride to a pint of water.   Among 278 patients so treated he had a death rate of 33·8 per cent., that of the preceding six years had nearly doubled this, being 61 per cent.

In 1912 Rogers devised his method of estimating the specific gravity of the blood by small bottles of glycerin and water of different degrees of concentration.   This was originally Lloyd-Jones's method ; Duncan White, in China, preferred (1912) a mixture of castor oil or olive oil and oil of wintergreen to Rogers's glycerin and water, because the blood does not mix with this as it does with the diluted glycerin.   Rogers's procedure was to give three pints in the collapse stage if the specific gravity was 1063, five pints if it was as high as 1065.   In the stage of reaction with deficient urinary excretion, he gave slow isotonic venous injection if the specific gravity was above 1060, subcutaneous injection if below 1060, till the blood was diluted down to a specific gravity of 1050.

Sometimes, owing to collapse of the vein walls injection *intra*

venam was not feasible ; under such circumstances T. H. Bishop, at the Lower Ganges Bridge works, was accustomed to give the hypertonic solution intraperitoneally with success. L. Gunguly, at the 'Campbell Hospital, Calcutta, reported 184 cases of severe cholera, of whom 144 or 78 per cent. were totally collapsed and pulseless on admission ; 108 or 58·6 per cent. of the patients recovered.

The rationale of saline injection had a threefold aim. First, to overcome acidosis. To attain this, each time infusion was indicated a pint of water containing 160 grains of sodium bicarbonate and 60 of sodium chloride was injected before the saline. Of the latter, hypertonic, some three pints were given slowly, at the rate of about 4 oz. a minute. Whenever the specific gravity of the blood rose above 1063 or the pulse was failing the injection was repeated. At the Calcutta Hospital by means of action on these lines the fatality rate was reduced by 75 per cent.

The second aim was to replace lost fluid and salt—by injection of hypertonic solution containing sodium chloride 120 grains, calcium chloride 4 grains, potassium chloride 6 grains to the pint of water. The theory is that water is drawn into the circulatory system and the blood pressure thereby maintained ; the injection is given at 10° F. above the body temperature. Thirdly, to neutralize toxins in the intestine. To this end calcium or potassium permanganate is given by mouth to oxidize the toxins and kaolin is added to absorb them. After the collapse stage is overcome, keratin-coated pills of potassium permanganate, 2 grains, are given every fifteen to thirty minutes till the stools become

Years.	Cases.	Deaths.	Mortality per cent.	Recoveries per cent.	Method.
1895–1905 .	1243	788	63·4	36·6	Normal saline, subcutaneously, and *per rectum*,
1906 . . .	112	57	50·7	49·1	Normal saline intravenously.
1907 . . .	158	94	59·5	40·5	Normal saline subcutaneously and *per rectum*.
1908–July 1909	294	96	32·6	67·4	Hypertonic saline, intravenously.
August 1909–1914	858	222	25·9	74·1	The same + permanganate.
1915–17 .	638	122	19·1	80·9	These, with alkalies.

greenish; calcium permanganate may be given to drink with kaolin suspended in water.

The table on page 689, adapted from Rogers's article on Cholera (Byam and Archibald's *Practice of Medicine in the Tropics*), shows clearly the relative mortalities under different methods of saline treatment.

Two years later, in 1919, Rogers's method was used in the Harbin epidemic. At the Chinese Hospital among 1962 patients so treated the fatality rate was 14·1 per cent. The Russians used normal saline subcutaneously and castor oil internally; at the Russian Central Hospital the fatality rate was 33·7 per cent. and at the Municipal Hospital 57·7 per cent.

(iv) Choleraphage

Here we shall speak of choleraphage only as regards its use in treatment of cases. Its use as a prophylactic is dealt with later. The number of deaths occurring in India from cholera is very high; between 1905 and 1916 the number so attributed annually never fell below 300,000 and in some years was twice this figure. It is much to be regretted, therefore, that the destructive action of bacteriophage *in vitro* has not received general confirmation when administered *in vivo*. According to d'Herelle phage is the therapeutic principle which develops in an infected individual and lies at the basis of natural cure. Applying this on a larger scale to the course of an epidemic the rise is due to importation of the causative organism and its spread by flies, food, water, etc. Convalescents develop and excrete bacteriophage which is spread in a similar way and as more and more patients recover so the more widely is the phage disseminated and the epidemic brought to an end.

The influence of bacteriophage on the course of the disease was studied in the Campbell Hospital, Calcutta, in seventy-three cases, patients being examined for bacteriophage on arrival, 10 to 20 hours after onset of their illness. Those having no bacteriophage died in a few hours. Previously, in 1921, d'Herelle had failed to isolate phage in 150 cases in Indo-China and all died; two were passing very active phage and although very ill both recovered. In three it was weak and became weaker till it finally disappeared and all three died; in thirteen it was weak at first but rapidly became stronger, attaining a maximum in 24–48 hours; all these recovered.

Investigation, notably by I. N. Asheshov (1930), showed that

there were strains or types of phage, each alone being inadequate but when acting in concert effective. Results of trial in the field have not been altogether convincing, though some striking results have been reported. Thus, in India in 1928, in four villages 107 received no phage and sixty-eight (63·5 per cent.) died ; forty-one received phage and only three (7·3 per cent.) died. The mode of administration was as follows : Two c.c. of culture were added to 10 c.c. of water and swallowed by the patient ; 4 c.c. in 40–50 c.c. water were left and a tablespoonful taken every hour. Next day, if the condition was still serious three doses of 2 c.c. were repeated. There was no selection of cases, those refusing the treatment served as controls. Twenty were so treated and six died (8·5 per cent.) ; 240 refused and of these 143 (60 per cent.) died. The conclusions reached were that the treatment is simple, inexpensive, causes no inconvenience, and the cultures keep well and can be sent to a distance ; but the effect depends, not on the amount used but on the virulence of the phage. Asheshov found three strains which he denominated A, B and C. If any was omitted the results were not good because after the initial lysis a secondary growth of vibrios occurred which had acquired resistance to the phage used, but when all three were combined lysis was complete and no secondary growth occurred. Asheshov found that type A will destroy the secondary organism which has resisted B and C, and similarly as regards the others. He found also that type A has the most rapid action, but is the least stable ; B and C are more stable but slower in action. In Puri in 1929 in cases arising among the pilgrims the treatment of actual cases in hospital with bacteriophage was disappointing, but it must be remembered that the multiplicity of phage elements had not then been determined.

5. PROPHYLAXIS OF CHOLERA

Prevention of cholera may be divided into three sub-sections : (a) the use of vaccines ; (b) the use of bacteriophage ; (c) general methods including quarantine measures.

(a) Immunization by means of what came later to be denominated *vaccines* dates from 1885 when Ferran administered living vibrios in Spain ; he injected subcutaneously the organism in broth. In many cases the reactions were severe and the method was suppressed by Government. Next came Haffkine's preparations in 1893. Haffkine prepared two forms ; one in which the vibrios were attenuated by special modes of cultivation, the other in which the virulence was exalted by peritoneal passage through guinea-pigs. Sometimes the former was given, at other times

both. The results were too irregular for satisfactory evaluation, but they sufficed to establish a presumptive favourable opinion. Later, he prepared another vaccine in the usual way, killing the culture by heat and preserving it with 0·5 per cent. phenol and its employment showed (Greenwood and Yule, *Proc. Roy. Soc. Med.*, 1915) that it " is a prophylactic step of importance, though an exact statistical measure of the degree of relative immunity conferred cannot be provided," owing to the conditions under which it had to be tried in the field.

In 1896 Kolle's vaccine came on the stage ; this was made from a twenty-four-hour agar culture, killed by heating to 55° C. for an hour and standardized to contain 1000 million organisms per c.c. It was given in two doses, 0·5 and 1 c.c., at a week's interval. It was held to be effective for six to twelve months.

Murata in 1904, during an outbreak in Japan, used this vaccine in doses of 1 c.c. and reported that among the inoculated the mortality [case mortality] was 45·5 per cent., among the uninoculated 75 per cent. ; the attack rates were 6 and 13 per 10,000 respectively. No serious reaction followed the injections. In the same year Strong carried out experimental work with a vaccine produced by ' autolytic digestion ' of cholera vibrios in water and reported good results in rabbits, in that it caused the appearance of bactericidins and agglutinins in their blood as marked as those following inoculation with living virulent cultures. We have seen no record of this being tried in human cholera.

In 1912–13 vaccines composed of living organisms attenuated by heat were employed by Nicolle, Conor, Conseil and others, but this method was not practised widely. We may here mention incidentally that in 1928 Fairbrother showed that in the cholera vibrio there were two types of antigen, of which the heat-stable somatic antigen plays a far greater part in immunization than does the heat-labile. In 1918 Shiga introduced the ' sensitized vaccine ' for which he claimed the advantage of producing immunity more rapidly. A certain degree of immunity resulted from a single injection, though two gave better and more lasting results. They were effective for eight months. Up to this time the Chinese had been importing vaccines, notably Haffkine's and Kolle's, but found in 1919 that they obtained better results from using vaccines prepared from strains isolated locally.

In 1919 T. C. McCombie Young reported the results of prophylactic inoculation of coolies going from Assam to Behar and Bengal. There was time for only one injection. In the two and a half months before inoculation was started the deaths from cholera-

among emigrants to Assam were 6·78 per thousand ; in the succeeding two and a half months among the inoculated they were only 1·8 per thousand, though the cholera epidemic increased steadily in the recruiting districts as was usual in Behar and Bengal at that time of the year.

A. Roy, the same year, announced that at a village near Hazariabagh, Chota Nagpur district, during the preceding two months 20 per cent. of the population had been attacked by severe cholera and all sanitary efforts met with obstruction on the part of the people. The Dublin University Mission staff began inoculation when the outbreak was at its height. Two days after the first injection a decrease was observed, and after the second, ten days later, fresh attacks ceased. He states that even the first injection seemed so convincing that thirty-six sceptics asked to be inoculated.

Japan in the 1922 outbreak arranged for all arrivals from infected ports to have fæces examined for the vibrio ; all found to be carriers were isolated and the people in the infected areas were vaccinated. It was reported that in the last outbreak in Korea 1,444,318 persons were inoculated " with good results." Most had two injections, but if this was not feasible a single dose of 1 c.c. produced only slight reaction and proved very satisfactory. [One would prefer some concrete figures to these indefinite statements.]

Attention should be called to a still more recent outbreak, that of Haiphong in 1937, where vaccine was used ; the sequence of events is instructive. The outbreak was a severe one and was made worse by the influx of refugees from the Japanese attacks. It had been in progress for some months and vaccination was begun on 23rd September, 1938, and in ten days, by 3rd October, 94,000 persons had been vaccinated. Later the number reached 158,000. By 13th October a steady decline in cases was observable. Of 546 patients admitted to hospital 94 per cent. had not been vaccinated. The vaccine was not used in the Tonking delta and the disease continued to prevail there, after it had been extinguished in Haiphong. The vaccine, therefore, certainly appeared to reduce markedly the prevalence, but no evidence was obtained of its mitigating the severity of attack if infection did occur.

In 1922 Besredka introduced his bili-vaccine for oral administration. The evidence adduced as regards this during the next five or six years was conflicting. In 1928 W. J. Vickers in Malay

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published an instructive comparison between the ordinary vaccine subcutaneously inoculated and Besredka's bili-vaccine administered orally.

1. *Ordinary, subcutaneous vaccine :*

One dose only (0·5 c.c. = 4000 million organisms) given to 17,160 persons. Of these the percentage attacked was 0·34 and the fatality rate among those attacked was 37·3 per cent.

Two doses (together 12,000 millions) ; 8485 persons. The percentage attacked was 0·37, fatality rate 6·5 per cent.

Not inoculated 29,254 ; percentage attacked 1·67, fatality rate 37·6 per cent. Thus the relative numbers of cases among the unvaccinated was 4·5 times as large as among the vaccinated and the percentage case mortality as compared with that among those receiving the two doses was as 5·8 : 1.

2. *Besredka's Bili-vaccine orally :*

The full course of three doses (= 200,000 million organisms) was given to 4982 persons ; the percentage attacked was 0·36 and the case mortality was 22·2 per cent. Of 11,004 untreated 2·02 per cent. were attacked and the fatality rate among these was 41·9 per cent. The number of cases among the unprotected controls was therefore 5·6 times that among the vaccinated and the fatality rate was nearly double.

It would appear from these figures that the full course of the bili-vaccine confers practically the same degree of protection as the ordinary vaccine administered subcutaneously, but the immunity conferred by a single inoculation is nearly as high as that from the full course of the bili-vaccine. The fatality rate, however, was 1·7 times as great after a single inoculation, but only one-third when the full dose was injected, as compared with the oral bili-vaccine.

The difficulty of interpreting satisfactorily and fairly the results of vaccines used prophylactically is made greater by the fact that an outbreak may die down spontaneously by the time the second dose is given. The following by Rogers and Megaw in their work on *Tropical Medicine* (1930), from a report by C. A. Bentley in India seems to confirm their value.

During a severe outbreak . . . the Hindus only submitted to inoculation and the disease ceased among them, but continued among the uninoculated Mohammedans. The Mohammedan males were then inoculated and the disease promptly stopped among them, but continued among the uninoculated females, and only ceased among them when they too were inoculated.

Mention may be made in passing of the antivirus of Besredka and Golovanov, introduced in 1923. There is no record of its use as a prophylactic. Their antivirus was prepared by filtering 8-10 day bouillon cultures of the vibrio, reinoculating with the organism and again filtering after another eight to ten days. We may also refer here to the use of serum for conferring passive immunity, introduced by Hetsch and Harvey in 1928-9, for it was employed therapeutically rather than prophylactically.

(*b*) We have spoken of the use of Bacteriophage—*Choleraphage* —in treatment of the disease ; we must again refer to it as it has been employed prophylactically. Field trials are not, on the whole, very convincing owing to the difficulty, almost impossibility, of setting up scientifically trustworthy controls. Lieut.-Colonel J. Morrison, I.M.S., claimed good results in Assam by adding the phage to water-supplies, but others, in Behar for example, were unable to confirm his results. To compare the fatalities in two epidemics, one in which the phage is used while in another it is not, is fallacious because the case mortality varies too widely in different outbreaks for the comparison to have any validity. Again, to add phage to the water-supply before a village is attacked is open to the rejoinder that the infection might not be introduced at all, or if it were the type might be mild.

Two examples may suffice to indicate the procedure. In 1927 in a village in India of 345 dwellings the water-supply consisted of nine private and thirteen public wells. On 2nd August there were six cases of cholera and three deaths and the next day six cases, two deaths. On 4th August 30 c.c. of potent bacteriophage were added to two wells in the contaminated area. There was only one case subsequently. On another occasion 40 c.c. of bacteriophage were passed into the water-supplies of ten villages in which cholera had existed for a long time with a high fatality rate ; " in a day or two the epidemic ceased." This seems to be too dramatic to be merely a coincidence.

It was tried again in Habiganj and Nowgong in 1934 and the conclusions, if we can so call the uncertain decisions arrived at, were that the use of the choleraphage when employed *alone* on a large scale as a preventive must be regarded as still *sub judice* ; that, as a means of limiting spread of the disease, bacteriophage alone is at least as effective as inoculation when the latter is used as a preventive measure after the appearance of the disease.

(*c*) *General Methods of Prevention and Quarantine.*—Though the fact that cholera in its spread followed the routes of travel

was known vaguely for many years before the actual cause of infection was discovered in 1883, until the vibrio was found and its mode of spread determined efforts on general lines of prevention met with little success. Thus never before had such combined efforts been made by the Governments of Europe to exclude epidemic disease as those exercised in 1830–1. Rules were made for isolation of the sick, for the burning of old clothes, for burial of the dead in special places; attendants on the sick were required to keep away from the rest of the community, food for those in infected houses was left in front of the dwellings and not taken in until the person delivering it had gone away, a police cordon reinforced by troops was placed around infected areas; all these regulations were enforced as rigidly as possible and, in Spain, the penalty for infringement was death. Nevertheless the disease continued to spread.

The possibility of infection arising from certain foods likely to be contaminated or to cause intestinal disturbance was clearly in the minds of the Washington Board of Health when they issued the following on 16th August, 1832:

The Board, after mature deliberation, have Resolved, and they do now declare that the following articles are, in their opinion, highly prejudicial to health at the present season. Believing them, therefore, in the light of nuisances, they hereby direct that the sale of them, or their introduction within the limits of this city, be prohibited from and after the 22nd instant, for the space of ninety days:

Cabbages, green corn, cucumbers, peas, beans, parsnips, carrots, egg-plants, cunblings or squashes, pumpkins, turnips, water melons, cantaloupes, musk melons, apples, pears, peaches, plums, damsons, cherries, apricots, pineapples, oranges, lemons, limes, currants, ice-creams, fish, crabs, oysters, clams, lobsters and crawfish.

The following articles the Board have not considered it necessary to prohibit the sale of, but even these they would admonish the community to be moderate in using:

Potatoes, beets, tomatoes and onions.

In small local outbreaks, however, disinfection often proved of the greatest value. Thus, in 1854 cholera invaded, or was introduced into, the prison at Naisheim. The sanitary condition of the gaol is stated to have been as bad as it could be. "The stools of the cholera cases and all others were subjected to disinfection and not a case occurred among the other prisoners." At Traunstein, Bavaria, "when sulphate of iron was employed as the disinfecting agent, the disease in every instance contented itself, contrary to its usual habit, with the first victim." This

seems too rash a generalization, too good to be true, but is so reported in the Constantinople Cholera Conference in 1868. In England Dr. Budd, in one outbreak at Horfield Barracks, near Bristol, reported excellent results from the following of his recommendation that the dejecta of all patients should be received into vessels containing a strong solution of chloride of lime, that soiled linen should be burned, latrines disinfected and that infected localities should be regarded as out of bounds for the troops, so that the soldiers might not wander there or visit people in them, and that the troops should be frequently inspected for discovery of any cases of the disease in its early stages.

There is a great tendency, in this as with other diseases, to confuse *post* with *propter*. In the Chile outbreak of 1886–7 great efficacy was thought to result from the doctors wearing caps and long aprons or overalls extending from chin to feet, and washing their hands and faces in corrosive sublimate, and from an order that all dishes used in the dining-rooms should be heated in flaming alcohol, and that all bread should be toasted.

About the middle of the nineteenth century, 1840–50, the general lines of prevention comprised house-to-house inspection to ensure cleanliness and ventilation, and public functionaries paid much attention to removing all evidences of dirt, on the principle that " all must be well where the eye finds cleanliness," or as we would say " what the eye does not see the heart does not grieve over," but, as Sir James Martin wrote, " mere overcrowding and want of ventilation have in recent instances enabled cholera to exert its worst effects." Free ventilation was insisted on, together with removal of obvious dirt, thorough cleansing of walls, floors, ceilings and furniture, and destruction of soiled clothes. Attempts were made to carry out these measures in all infected parts of the country, for it was generally believed that if the ' morbid matter ' was allowed to survive in a single district throughout the winter and early spring it would increase there and again spread.

' Houses of Refuge ' in towns received the healthy in poor and crowded areas while ' other asylums ' were provided " for those already labouring under cholera." Precautions were founded on the belief of dissemination of human intercourse, or that discharges from the alimentary canal, either by vomit or excreta, contained the cholera poison " although the theory based on that view has been found generally untenable and, at most, susceptible of very partial application " (Martin).

Other general measures recommended were soaking of soiled

linen, bedding, etc., in water to which some disinfectant had been added ; protection of food and drink from discharges, while nurses and attendants were advised to wash their hands before taking food (these have been referred to above as recommendations in the first place by Dr. Budd).

Quarantine, it was said, should no longer be adopted because it " interferes with commerce and has often failed because it was evaded and infected clothes are conveyed on shore." In August 1832, the Washington Board issued the following :

> All theatrical performances or other exhibitions which might be calculated to bring together large collections of persons be suspended for ninety days. Also
>> *Resolved,* that it is the opinion of the Board of Health of this city that quarantine regulations interdicting the commercial intercourse of our country are wholly ineffectual in preventing the introduction and spread of Asiatic cholera, as well as vexatious and embarrassing to the community, and that they are injurious by creating a false confidence in such provisions, to the neglect of the more important preservatives from the disease. The Board therefore earnestly desires that the city authorities will not enact any prohibitory regulations upon this subject.

But, quarantine restrictions being abrogated, each ship coming from an infected port is advised to bring an official certificate of its having been inspected and found cleanly and not overcrowded and the crew healthy at the time of sailing.

In the Army, with which Martin was more familiar, the measures he advised were the enforcing of rules for careful and frequent inspection of the men and their quarters. " Each soldier is to be provided with two cholera-belts as part of his necessaries," but flannel waistcoats, " if thought necessary for individuals," are to be provided at their own expense. Men attacked were to be isolated while as for contacts every effort should be made to " amuse and occupy the minds of the soldiers by trap-ball and other games." Overcrowding was a thing to be avoided and great attention was to be paid to cleanliness and ventilation ; floors and passages were directed to be " dry-scrubbed, not washed " [no reason for this distinction is given]. The quality of the beer to be issued to the soldier is to be " ascertained by a competent person " [but as to who this is or how the lucky man was to be selected he is again silent] and the acid in porter or ale is to be corrected by the addition of chalk or carbonate of soda —thus spoiling good beer.

According to his recommendations the clerical returns bulk

largely, for " from the moment a case of common or spasmodic cholera occurs a daily report is to be forwarded to the Director-General until further orders " and " a full report of each case among the troops with details of previous habits, intercourse, diet, exposure to cold, wet, etc., and other particulars is to be forwarded to the Director-General." One hardly knows whom to pity most, the harassed medical officer who tried to do this in the intervals or course of his arduous duties in attending to the victims in an epidemic, or the Director-General who felt it his duty to read them and take action on them.

When the causative organism, its characters and mode of propagation became known measures had to be modified. Thus, at the beginning of the present century the disease in the Philippines was combated by isolation of patients, inspection of districts to discover cases either overlooked or hidden, closing of wells and distribution of pure water, guarding of the river water-supply by troops to prevent its being contaminated. Buildings in small districts which were heavily infected were destroyed by fire, compensation being given to the owners. The water-supplies were repeatedly examined bacteriologically. Uncooked foodstuffs and fruit were prohibited for sale in open markets as infection might readily be spread thereby. Protection of food from flies was strongly urged and prophylactic inoculation was widely practised. It was reported later that the incidence among the inoculated was only one-sixth that among the uninoculated.

Passing now to Quarantine in more detail. According to Geigel Denmark was almost free from cholera in 1830 when quarantine rules were strictly enforced and he attributes the freedom to the quarantine, for in 1852 the ' miasmatic view ' held by many medical men led to the abolition of quarantine and in the following year Copenhagen suffered severely from an epidemic.

A quarter of a century later as a result of the resolutions passed at the Vienna Conference in 1854 the following may be taken as summing up the rules as regards quarantine :

1. Ships from infected or suspected ports, or which have touched at such a port or communicated with an infected ship, or have had suspected cases on board are to be medically examined as to the state of health of the personnel, crew and passengers.

2. The bodies of any dead of cholera are to be taken ashore and buried at once ; any sick are to be isolated and the others disinfected ; also their clothes and effects and the ship itself and any cargo landed.

3. Vessels from infected ports are to be kept under observation for periods up to a week (in exceptional cases ten days) according to

the length of time since the vessel left the infected port ; or, if a case has occurred during the voyage or on the day of arrival, surveillance for a week from the date of isolation.

4. Special regulations were to be made in the cases of emigrant or pilgrim ships.

5. In ports where cholera is epidemic there need not be special quarantine, but disinfection has to be carried out.

By an Order of 1888 the Port Sanitary Authorities were given certain powers. Under the Quarantine Act all disease on board vessels entering a port, not arriving coastwise, had to be reported to the Customs and the vessel was detained until released by the officer of the Sanitary Authority. A vigilant observation is kept of records of cholera in foreign countries, the earliest possible information is obtained from the Customs of arrivals of infected or suspected vessels, printed information is published in the port on *Cholera and Its Prevention*, a careful inquiry is made into the water-supply of the ship and cases of sickness on board, in particular of diarrhœa, and special accommodation is provided for cases of cholera.

The measures for controlling the spread of sea-borne cholera do not differ in principle from those applicable for land-conveyed infection. The menace is reciprocal ; on the one hand conveyance to the land by the crew or passengers of an infected ship and, on the other, contraction of the infection by healthy seamen going ashore at an infected port.

The general rules of the National Quarantine Service of China as regards an *infected* ship or one supposedly infected are :

1. It should be medically inspected.

2. Those actually sick and any suspects should be disembarked and placed in isolation.

3. The crew and passengers are kept under observation for not more than five days. Any found by bacterial examination to be carriers (*i.e.* passing the vibrio) are kept until three examinations carried out on successive days yield negative results.

4. Bedding, soiled linen, wearing apparel, etc., are disinfected.

5. The entire vessel or such parts of it as the Quarantine Officer considers contaminated must be disinfected.

6. The unloading of the ship has to be performed under supervision and those taking part in the unloading should have been immunized ; they must further be kept under observation for five days after conclusion of the unloading.

7. If the drinking water on board is not above suspicion, the receptacles and tanks must be emptied and disinfected and a fresh supply obtained.

8. Water ballast must be disinfected before the vessel receives its discharge.

9. Human dejecta must be disinfected before being discharged into the waters of the port.

If there is no history of any case or suspected case of cholera on board nor any sign of the disease, but the vessel has come from an infected port, the above rules are modified and only the first—medical inspection—and the last—water-supply, disinfection of water ballast and of dejecta—need be carried out.

It is difficult to assess the part which quarantine measures have played in reducing the incidence of cholera. *Post hoc* the improvement is marked, but *propter hoc* is far from certain. Experience has shown that the disease may from time to time take on an explosive and dispersive character ; experience has also shown that diseases may change their nature—scarlet fever is not the frightening disease in the first quarter of the nineteenth century it was in either the preceding or succeeding twenty-five years, after which it has seemed to decline steadily in severity ; smallpox has become, in England at least, so mild that it is dreaded less than vaccination ; in some of the Colonies the mild form, *alastrim*, seems to have almost replaced the old variola, with its confluent and hæmorrhagic types—may not cholera have undergone a spontaneous change of type ?

Quarantine for cholera no longer exists in Great Britain ; it has been replaced by the Cholera Regulations under the Public Health Acts of 1896 and 1904. The powers conferred by these regulations, in conjunction with good port sanitation, control over immigrant aliens and their entry into this country (Great Britain) and the ability to prohibit the importation of rags from infected ports are the chief preventive measures maintained. These Regulations are in the main those quoted above as holding good for China, in fact the Chinese Quarantine Regulations are based on and constitute a somewhat amplified form of the Regulations —amplified, that is, to suit local conditions.

Though the strict regulations of the past have now become so greatly modified the present state of comparative freedom from the disease must be attributed to these past restrictions and rules —the reorganization of the Public Health Service, introduction of piped water-supplies, vaccination on an extensive scale, the need of certificates of vaccination from immigrants and pilgrims, and strict quarantine regulations.

CHAPTER XII
PLAGUE

1. INTRODUCTORY

In attempting to give an account of plague in a work dealing with the evolution of tropical medicine we are at the very outset confronted with the difficulty of deciding at what period in the world's history we ought to start. Its distribution has been world-wide ; now, with a few exceptions it has become mainly a tropical and subtropical disease. It would, however, convey a very biased view if we disregarded it except in so far as it concerned warm climates and in the following account we shall have a good deal to say on plague in general and not confine our remarks to it as a tropical disease.

Plague can be traced back almost uninterruptedly to the third century before the Christian era when Dionysius told of it as a fatal disease in Libya, Egypt and Syria, and Homer's story would carry us some 900 years farther back. There can be no doubt that the epidemic in Libya described at the beginning of the Christian era by Dioscorides, a Greek surgeon to the army in the time of Nero, and Poseidon, a physician of Alexandria, was true bubonic plague :

> Dioscorides autem et Posidonius plurima de hac re enarrant in libro de peste, quae eorum aetate in Libya adfuit ; illi autem accedere dixerunt febrem acutam, dolorem, perturbationem totius corporis et delirium et bubonum apparitionem magnorum et durorum, qui in suppurationem non transiebant, non solum in solitis locis verum et in poplitibus et cubitis ; quamvis illic omnino tales inflammationes non solent observari ; fortasse autem buboniformis morbus Hippocratis constitutionem dictam indicat ; aderit autem nonnunquam et in genitalibus talis bubo, itu et ulcus pestilens et febris quam pestilentem dicunt ; plerumque epidemica talia sunt, ita ut communia sint omnibus aetatibus et constitutionibus in nonnullis anni temporibus praecipue occurentia. (Rufus, translated by Bussemaker and quoted by Hirsch. Rufus of Ephesus lived in the reign of Trajan, A.D. 98–117.)

Poseidonius says later : " One can see an approaching plague by paying attention to the ill conditions of the seasons, to the

mode of living less conducive to health and to the death of animals that precedes its invasion."

Nearly 300 years before, Dionysius had noted what Rufus in the Collectanea of Oribasius, physician to Julian the Apostate (A.D. 355–63), speaks of as "pestilentes bubones maxime lethales et acuti, qui maxime circa Libyam et Aegyptum et Syriam observantur." Prior to this Homer described plague among the Greeks at the siege of Troy (1184 B.C.), ascribing it to the wrath of Apollo who was angered at an insult to his high priest Chryses, and also to the god's malevolence and disgust at the filth lying about the camp ; Agamemnon orders the refuse to be thrown into the sea. This would seem to be the earliest instance of sanitary reform known, at least on record, discovering and seeking to remove the cause of pestilence and overcome the lethargy of ignorance and credulity.

That plague has become more a tropical disease is largely a matter of chance, because in warm climates there are better opportunities for rat-fleas to bite man who in these regions is scantily clothed ; also the dwellings of the natives are insanitary and often overcrowded and rat migration is less. Where the latter conditions prevail, as in parts of Siberia and North China, the disease is as prevalent and spreads as rapidly as in tropical regions.

To come nearer to our own times, plague has within the last 600 years devastated the Continent and again and again invaded and wrought havoc in Great Britain. These outbreaks we shall not describe ; even had they not been recorded and studied they would be outside the scope of the present work. Incidentally, the Passion Play at Oberammergau which till 1930 had been a decennial event owes its origin to plague which visited this part of Bavaria in 1633. Gaspar Schneler, a native of Oberammergau, but living, in 1633, at Eschenlohe, where plague was rife, wished to visit his family. He carried the infection to Oberammergau and died of it there, and during the ensuing thirty-three days eighty-four deaths occurred there from plague. A meeting of the inhabitants was summoned and six men and twelve women took a solemn vow to produce every ten years a play on the Passion. The plague, it is said, ceased at once.

It is not probably known that commemoration of an outbreak in 1666 in a village, Eyam, in the Peak district of England is still held. In that year, out of a population of 350 plague killed 260 and the cottage where it started still is known as Plague Cottage. History records that the rector, William Mompesson, and his wife

Catherine nursed the afflicted day and night and among the victims was Catherine Mompesson whose grave is still shown.

Earlier in the same century the continued presence of plague in England was the reason for ' Bills of Mortality ' which developed into the science of Vital Statistics. Plague was never away for long from Great Britain and London from the fourteenth to the seventeenth centuries ; in fact, the fire of London of 1666 was the eliminator of the plague of the preceding year. Though isolation and quarantine had been applied in Tudor times, the prevalence of the disease was not really known. Persons were delegated to be on the look out for cases and to report any discovery to the Parish Clerks—men who were first appointed in the time of Thomas Cromwell to keep the parish registers. To enable this to be done ' searchers ' were deputed to see every case of death and send to the clerk lists of deaths and the causes, noting in particular any due to plague. The weekly lists compiled from these returns were the first ' bills of mortality.' They were not very accurate, as one would infer from the fact that the ' searchers ' were not medical men, and might even be ignorant. old women [so it is said, but in those days such would not know how to write and send in their returns]. At the beginning of the seventeenth century the ' bills of mortality ' were more regularized and continued until they merged into the Registrar-General's returns towards the middle of the nineteenth century (1842).

The ' bills ' had been utilized for enforcing isolation of plague cases and contacts ; later they served as a means of warning, for when cases began to show increase in numbers in London the King and Court would leave for the country and stay there till the danger was thought to be over. The ' bills ' gained in importance after John Graunt, a draper, in 1662 published his *Natural and Political Observations* upon them ; this was really the first book on Vital Statistics.

Two or three further points of general interest may be touched upon by way of introduction before we consider in detail plague, its history and the methods of dealing with it in tropical countries.

The Black Death (the adjective implying ' gloomy,' ' grievous ' or ' lamentable,' *cf.* ' Black Monday ') of 1346–55 found an entirely susceptible population in Europe ; hence its appalling ravages. The merest sketch must suffice here. There was much dispute as to its starting-point. Russian records placed it in India, Greeks said it was Scythia, the British assigned it to India and Asiatic Turkey, and the Arabians to Tartary. The Italians regarded

Cathay (Northern China) as the primary focus whence it spread in all directions, to the Black Sea by Bokhara and Tartary, to India, the Caspian and Asia Minor, to Baghdad, Arabia, Egypt and Northern Africa.

The most common belief was that it started in China, passing west to Egypt and Constantinople and thence into Greece, Italy, France and Africa; from the Mediterranean coasts to Great Britain and from Britain to Germany, Hungary, Poland and Denmark. Greenland is said to have been depopulated and all the mercantile class was killed off. As regards England most historians are agreed that it started on the coast of Dorset in 1348 and soon spread through Devon to Somerset and all over the country and was the worst since that of Vortigern's time mentioned by Bede. Thirteen acres of ground near Smithfield were purchased by Sir Walter de Maunay [some give the name as Sir William Manny] and 50,000 were buried there; from Candlemas to Easter some 200 a day (Lyttleton); at Leicester there died 700 in one parish (St. Martin's), 400 in another (St. Cross) and 380 in a third (St. Leonard's). In the city of London, according to Crutwell's Gazeteer, 100,000 perished.

The Scots, invited by the prospect of an easy prey in this season of death and desolation, made an irruption into the northern counties, and, together with a large booty, carried back the contagion to their native country where it raged with uncommon violence (Lyttleton).

At Oxford the schools, colleges and halls were closed and, according to Knyghton, the pestilence had swept away so many priests that a chaplain could hardly be got to serve a church under ten marks or ten pounds per annum; and men would hardly accept of a vicarage of £20 per annum, because of the greater danger from stricter residence. In Florence 60,000 died, according to Antonius, the Archbishop there, among them the historian, John Villanini. Other figures given are : Venice 100,000, Lübeck 90,000, Avignon 62,000, Marseilles 60,000 in one month, Paris 50,000, Norwich 50,000. Germany 1,244,434 (Short); Spain " two-thirds of the population." Guy de Chauliac, physician to Pope Clement VI, was at Avignon in 1348 and he says: " The father refused to visit his son and the son his father. Charity was dead and hope downcast." With him discretion was the better part of valour and he advised flight from Avignon and the taking of aloes. For those unable to seek safety by flight he advised venesection; purification of the air by fires, the use of treacle, apples and savoury things to comfort the heart, and bitters to prevent putrefaction. Should this not suffice and the individual be attacked, the patient

was to be bled, purged and given electuaries and cordial syrups; buboes were to be ripened by application of poultices of figs and boiled onions pounded and mixed with leaven and butter. Carbuncles were to be leeched, scarified and cauterized (Raymond Crawford, *Plague and Pestilence in Art and Literature*).

This was the pestilence that Boccaccio, Petrarch and Wycliffe speak of. It died down probably from want of victims, but smouldered on, breaking out again in 1361, 1371, 1382, and thereafter at intervals till the end of the eighteenth century, latterly with diminishing intensity. Russia and the Caucasus continued to suffer till 1820. It has been stated, though there is no confirmatory proof, that altogether in the Black Death 25,000,000 perished. Incidentally, it was during this epidemic that quarantine became a recognized procedure in Europe.

Certain outbreaks in English schools in the fifteenth to seventeenth centuries, mentioned in the Medical Research Council's Special Report (No. 227, 1938) on *Epidemics in Schools*, are worth passing notice as of some historical interest. Winchester was the scene of several. Thus in 1430–1, twenty-six of the scholars and eleven on the staff died of plague. Other outbreaks occurred in 1492, 1509, 1516 and in 1543. The last was the occasion for acquiring a house at Moundsmere, twelve miles distant, for segregating patients and down to 1887 as one of the terms of agreement the tenant was required to set aside part of the building for the use of College boys " to avoid plague or any such pestilential sickness."

At Eton also outbreaks of plague necessitated the boys being removed on several occasions : in 1509 to Langley, in 1537 to Hedgerley, in 1564 to a farm building at Cippenham, and down to 1884 the tenant was bound by the terms of his lease to take, if required, six boys free of charge for three months. Finally, in 1690 an infirmary was built to accommodate a dozen patients. In 1556 both at Eton and at Winchester there was chosen a *Prepostor Immundorum* whose pleasant duty it was to watch for " yll kept hedys, unwashed faces, fowle clothes and sich like " (Mackyn's Diary).

In 1605 plague was so severe that Westminster school was closed for six months and at Oundle, in Northamptonshire, in 1666–7 a pest house was provided and the school closed for six months.

Defoe has written a vivid account of the Plague of London in 1665, but, though the book is called a *Journal of the Plague Year*, 1665, we must not regard it as factual. His picture is more true

of the 1720 outbreak in Marseilles than of the London epidemic. It is known that he carefully collected material for a diary of the Marseilles outbreak. He was born in 1659 and was, therefore, only six years old at the time of the London epidemic and his book was published in 1722, two years after the Marseilles outbreak. The work has been, and is even now, widely read and is taken by most as true of the London plague ; probably the events recorded actually happened but there has been a ' change of venue.'

In this Journal Defoe refers to the belief that infection was often spread by contagion of the human breath and that the practice of using perfumes, aromatics and essences came into vogue on that account. He states that on going to church where many people were present

there would be such a mixture of smells at the entrance that it was much more strong, though perhaps not so wholesome, than if you were going into an apothecary's or druggist's shop. In a word the whole church was like a smelling bottle : in one corner it was all perfumes ; in another aromatics, balsamics, and a variety of drugs and herbs ; in another salts and spirits ; as everyone was furnished for their own preservation. . . . The poorer people, who only set open their windows night and day, burnt brimstone, pitch and gunpowder and such things in their rooms, did as well as the best.

At Aleppo where plague prevailed tobacco was thought to be preventive and women as well as men smoked ; according to Dienerborch, and Chenot and Riverius, smoking " soothed the mind and rendered it less prone to the anxious fear which unquestionably excites infection." We find also in *Reliquæ Hearnianai*, 1665, that

none that kept tobacconists' shops had the plague. It is that certain smoaking is looked upon as a most excellent preservative. In so much that even children were obliged to smoak. . . . That year a school boy at Eton . . . was never whipped so much in his life as he was one morning for not smoaking.

Contrast this with Charterhouse in 1881 when a boy was expelled for smoking.

From the middle of the eighteenth century only the south-eastern parts of Europe formed a permanent focus of the disease. In 1841 it left Turkey and soon after became practically extinct in the Near East and the old ' Levantine plague ' vanished. New centres, however, sprang up, such as Assyr in Arabia in 1853, Benghazi in Tripolitania five years later (1858), Persian Kurdistan after the same interval (1863) and Mesopotamia in 1866–7. The

outbreak on the Volga at Vetbianka (1878–9) was probably connected with the Kurdistan and Mesopotamian centres.

Retrogression of plague from the West is ascribed to the march of civilization, higher standards of cleanliness and sanitation generally and better housing, together with legalized prophylactic measures (see later). " The abandonment of the Mediterranean as the centre of commerce for Europe, the shutting up of the Levant as the highroad for conveyance of produce of the East to the West, and the transfer of commercial activity to Amsterdam and London, whose connections were by sea and not by land, and consequently the avoidance of the former intimate connection with endemic centres," these are the reasons generally adduced.

Liston stated in 1904 that disappearance of plague from Europe in the seventeenth and eighteenth centuries coincided in the main with disappearance of the house rat (*R. rattus*) and its replacement by the sewer rat (*R. norvegicus*), but prior to this there had been a noticeable recession of the disease from most parts of the Continent. In other words, progress of civilization with better standards of living and less intimate contact between man and rats and fleas were only auxiliary, though potent, for before they came into force, at all events in large degree, plague had disappeared from parts of Europe and was leaving others. In fact, it must be confessed that the disappearance of epidemic plague from Europe remains one of the " unsolved mysteries of epidemiology." Even in the last quarter of the seventeenth century it was widely observed that plague was retreating from Europe. The last epidemic outbreaks recorded in the different countries were : Denmark 1654, Sweden 1657, Italy 1657, England 1665, the Netherlands and Belgium 1664–6, Switzerland 1668, France 1668, Germany 1679–81, Spain 1677–81. Turkey and the country immediately adjacent were almost the only seats of plague in Europe during the eighteenth century and thereafter the *fons et origo* of almost every invasion was Turkey.

2. Epidemiology

From the fifteenth to seventeenth centuries plague was with varying intensity habitually present in North Africa, Egypt, Western Arabia, Syria, Palestine, Asia Minor, Mesopotamia, Persia, probably India, China and Europe in general. From the middle of the seventeenth century the area of prevalence began to diminish. In the eighteenth century there were only two serious outbreaks known, namely from 1703 to 1713 involving Turkey, Hungary,

Austria, Eastern Germany, Poland and Russia; and the second in Provence from 1720–2. A hundred years later its area had shrunk to the easternmost part of Turkey in Europe and by 1841 it may be said that epidemic plague had disappeared from Europe, by 1843 it was no longer in Asia Minor, Syria or Palestine, and by 1844 had left Egypt. It has since then reappeared several times in Persia and the East but has not assumed an epidemic form to any extent.

While not attempting to go deeply into the question of plague in Europe we feel that a few words are called for even in such a work as the present. Whether the ' pestilences ' of the early years of the Christian era were or were not plague there is not satisfactory evidence to judge; there is no doubt, however, regarding the plague of Justinian, A.D. 543 which went by the names *pestis inguinaria, pestis glandularia,* and later *clades inguinaria* and *pestis bubonica,* and which is believed to have reached Europe from Egypt through Syria and the northern coast of Africa, and persisted for fully half a century, over-running the East and West, " depopulating towns, burning the country into a desert, and making the habitations of men to become the haunts of wild beasts."

In 1575 Sicily was attacked and from there infection was carried to Malta. In 1592 there was another serious outbreak and among a population of 40,000 there were 3000 deaths in fifteen months and it was the reason for erection of churches such as those dedicated to St. Roc at Valletta, Birkirkara, Balzan and elsewhere. It was at this time that wooden huts were erected for use as a lazarette on Bishop's Island (now Manoel Island); they were replaced by stone buildings in 1643.

In 1675—ten years after the plague of London—Malta experienced the worst epidemic on record. Starting in December it had killed by the following August 11,300 out of a population of 70,000, and among the victims were sixteen surgeons, ten physicians, over 1000 hospital attendants and many priests. It is said that the first medical work to be published by a Maltese was that by Laurentius Haseiah (or Haseiac) on plague in 1677, *De Postrema Melitensi Lue.* It is written in Latin and notes " bubones alias ad inguina, rarius sub alis, rarissimi sub auris." Thereafter it receded and in the Mediterranean in the nineteenth century the only outbreaks of any degree of gravity were those in Malta (1813), Gozo (1814), the Ionian Islands and the port of Noja in Italy (1815) and the Balearic Isles (1820). The first of these was very serious and was the cause of an acrimonious dis-

cussion as to whether plague was 'contagious' or 'infectious.' The disease was thought to have been introduced by vessels coming from Egypt ; it was raging in the Levant and owing to most of the continental ports being closed to British vessels trade between the Levant and Malta was brisk. Passengers and crews reached the island plague-stricken, and the cargoes of grain, fodder, cloth, etc., harboured rats and their fleas. Between the middle of April and the end of November there had been 4486 deaths in a population of 96,400, and in July fifty and even more were dying daily ; the town of Manderaggio had to be evacuated. Agostino Naude wrote a treatise on this epidemic (in Latin) and Baron de Piro and several army surgeons published their observations and comments. Since then the island itself has been free ; occasionally a case arrived on board but was removed to the lazaretto. In 1837 a hospital was erected on Manoel Island and since 1840 any such patients have been admitted there.

Quite recently, in 1936, there was a small outbreak between March and November, twenty-eight persons being attacked and eleven dying. Plague was rife among the local rats and the first three cases were traced to a stable, the rats of which were found to be infected. It was believed that infection had been introduced in bales of hay and straw from Northern Africa.

Vienna, situated on the river highway between east and west, was for centuries the home of plague, in fact one of the synonyms of the disease was the 'Viennese death.' Venice also was very open to plague infection owing to its being a busy centre of oriental commerce in the fourteenth to sixteenth centuries. It was the starting-point of two main sea-trade routes : 1. To the East, down the Adriatic, past the Ionian Islands, round Cape Matapan to Crete, and then branching in four directions : (i) To the Dardanelles, Constantinople, the Black Sea and the Sea of Azov. (ii) Along the shores of the Morea through the Ægean to the Dardanelles. (iii) To Asia Minor—Smyrna, Aleppo, Cyprus, Syria, Alexandretta and Beirut. (iv) To Alexandria and Egypt. These two last linked Venice up with the caravan routes from Ormuz in the Persian Gulf to Aleppo and Beirut and from Suez to Alexandria and thence to Persia, India and the Far East.

2. Westerly, by the Adriatic to Sicily and thence either to Tunis, Tripoli and Spanish ports, or by the Straits of Gibraltar to Great Britain and Flanders, bringing London and Bruges in touch with the East.

Venice also was connected with central Europe by land routes, by the Ampezzo Valley to the Pusterthal, Innsbruck and Munich,

and along the Po to Brescia, Bergamo, Lake Como and the Splügen Pass to Constance and on to Northern Europe.

The epidemic of 1679 is one of the best known in history. Sanitary conditions of the time were appallingly bad, the streets received the domestic garbage and refuse and there were no sewers. The city was more than usually crowded because that year was one in which several ambassadors with their retinues arrived— a Tartar embassy in March, the Papal ambassador with fifty six-horse carriages in June, the Russian ambassador with 200 attendants in the same month, and the Polish ambassador, Prince Radziwill, in July. Bodies dead of the plague (there was probably some typhus also) accumulated for want of people to remove them and dig their graves. Criminals were freed from gaol for this purpose.

To come to Britain. From quite early times down to the latter part of the seventeenth century plague was one of the endemic diseases of this country and the ' Great Plague ' of 1665 was but the last and biggest of a series of outbreaks. The Black Death has been referred to already. Plague was bad in England in 1532, 1535–6, and in an outbreak in 1625 deaths from the disease in London reached 4000 in a week. At that time the standard of living was low. Hordes of black rats infested the dirt-whelmed lath and plaster houses. We have already noted that the epidemic of 1532 led to the first issue of Bills of Mortality.

After the Great Plague of 1665 250 years passed without any visitation of note in England. Then in 1906 in the district near Ipswich and Felixstowe towards the end of the year numbers of dying and dead rats were seen and soon afterwards eight persons in one household were taken ill with symptoms which were diagnosed as pneumonia, and five of them died. For three years nothing more is heard ; then another household of eight, living in a dilapidated vermin-infested dwelling, within a couple of miles of the former cases was attacked and five of these also died. These patients had swollen and painful glands. A few months later seven persons living near were attacked with symptoms suggestive of pneumonia, and three died, followed a few days afterwards by the death of a woman who had attended them. As Greenwood records (*Epidemics and Crowd Diseases*) examination of the sputum of one of the patients revealed the plague organism. Inquiry led to the discovery of rodents dying in unusual numbers in the

district.   Rats caught were found plague-infected.   In the ensuing eight years rats, rabbits and ferrets were also found infected and in 1911 and 1918 human beings were attacked and died.   It was thought that infection had been introduced by rats in grain-ships, or by fleas in the grain brought by ships from the Levant.

Strange to say the history of plague in China does not extend as far back as one would expect and thus differs from cholera. The Chinese term for plague is Shu-yi and has not been traced earlier than A.D. 610.   The term means ' rat pest '—a remarkable forestalling or foretelling of twentieth-century knowledge.   It is mentioned in *Ping-Yuan* or *Sources of Disease* written by Ch'ao Yuan-fang.   Nevertheless Dr. Wu Lien Teh in the book on plague issued by the Chinese National Quarantine Service, giving a list of ' pestilences ' summarized from the Imperial Encyclopædia of K'ang-hsi, Peking, speaks of an extensive epidemic in 224 B.C. and mentions 232 outbreaks in different parts of the country between the years A.D. 37 and 1726, the date of the Encyclopædia. Of this list an outbreak in A.D. 1644 at Lu-an in the Shansi Province is noteworthy in indicating the presence of pneumonic features in some of the cases.

Since 1726 outbreaks in different provinces have been many and it would serve no useful purpose even to enumerate them. Plague broke out after the Taiping rebellion and when in 1894 it appeared in Kwang-tung more than 100,000 are said to have died of it, and later the infection spread to Hong Kong and Huichow.·   The disease had appeared in Yunnan in 1893 and by May 1894 reached Canton where among a population of a million and a half 70,000 fell victims (some say 100,000). In Transbaikalia between 1863 and 1928, a period of sixty-five years, there were seventy-five outbreaks recorded, most of the cases, the initial cases certainly, were bubonic and many axillary due, as we shall see, to handling of infected tarabagan.   Nevertheless in this territory started the extensive pneumonic outbreaks of 1910 and 1920, known respectively as the First and Second Manchurian epidemics.   In 1910 there happened to be a growing demand for skins of the tarabagan, *Arctomys bobac*, the price rose fourfold and in consequence many new and inexperienced hunters came to Upper Mongolia, Transbaikalia and Manchuria.   Those of experience took care to avoid animals which were sluggish —they were sick animals—whereas the newcomers were only too glad to make easy captures, were bitten by the fleas and contracted plague, axillary buboes being common because the bites were often on the hands and arms.   The men lived partly in underground

shelters and were much crowded. The disease spread eastwards to Tsitsikar (Heilungkiang Province), north to Mergen and Harbin, and south to Shuangchingpu, Chongchun, Mukden, Dairen, Tientsin, Peking (now Peiping), Tsinan and Chefoo. In seven months it travelled 1700 miles and killed 60,000 persons.

The Second Manchurian Epidemic of 1920 was due to a different cause, namely to civil war and the conditions associated therewith, overcrowding of troops, insanitation, unchecked trans-border traffic. At the outset a few cases were seen and control was attempted but the soldiers were somewhat unruly and out of hand. It is said that two of the contacts were allowed by the soldiers to escape and they went to the coal-mines of Dalainor, 100 miles west of Hailar, where the first cases occurred ; there they infected others in the crowded underground dwellings and the epidemic was fairly started. More than 1000 of the 4000 miners died and Harbin became the central focus. Thence it travelled east by the railway and in two months reached Vladivostock. The victims numbered 9300, of whom 600 were Russians.

The prevalence in Hong Kong is particularly interesting to us as it is a British colony and it was there that the causative organism was discovered. From 1895 to 1903 plague was present every year, with wide ranges of intensity, and a fatality rate varying between 80 and 97·7 per cent. In successive years from 1895 the numbers of human cases recorded were : 44, 1204, 21, 1320, 1486, 1087, 1651, 572, 1415, 506, 327, 893, 240, 1073, 135, 25, 269, 1857, 408, 214, 144, 39, 38, 266, 464, 138, 150, 1181 and 148. From 1924 to 1927 inclusive there were few cases, in 1928 four and in 1929 two and thereafter none. This disappearance is not easily explained, for the people, their customs and their dwellings have remained as before.

We must mention, however, that in the eighteen-nineties there was no restriction on vessels either coming to or leaving Hong Kong which thus became, as it were, a distributing centre of infection, whence the disease was spread to various parts of the world except China where infection traceable to Hong Kong was practically confined to the provinces of Kwangtung and Fukien. In Fukien there were no railways and foci were all contiguous to rivers and infection spread up them by the agency of shipping and junks. Newchang in Southern Manchuria was infected in this way in 1899.

Here is a convenient place to interpolate a few words on Dr. (later Sir William) Simpson's work on plague in Hong Kong in 1903. For a time it caused no little consternation because of the

greatly enhanced difficulties in prevention had his dicta been correct. He maintained that horses, cattle, pigs, fowls, dogs and cats were all infectible, that many of them might show no signs for three to four weeks after infection and then die of plague, and that their excreta contained plague bacilli which infected the soil. When rats—at all events rodents—were the only animals to be seriously considered the question of prevention, though difficult, was, compared with what it would be if Simpson's statements were correct, a fairly simple one, but now it would be of no use killing the rats on board ship when live fowls, turkeys, geese, pigs, sheep and other animals brought on board for human consumption were possibly infected and, by their excreta, infective. He used human temperature charts and any animal with temperature above 98·4° F. was febrile, and if this followed injection of the organism the ' fever ' was regarded as due to plague. He further maintained that men and animals were going about in Hong Kong plague-infected but showing no symptoms.

As in the case of cholera, so with plague ; its chief home in the British Empire is *India*. It was the discovery of an endemic focus of plague in the mountainous districts of Hindustan in 1815 that led to a reconsideration of the notion which prevailed up to that time that all outbreaks originated in Egypt or Syria. Later the observation was made that outbreaks might occur in other parts of the world while these places were not attacked. Within the past hundred years there have been several epidemics in India of varying intensity and range. That of 1896 was probably one of the worst. Infection was brought from the Far East to the docks at Bombay and spread thence through the Bombay Presidency, the Punjab and the United Provinces, killing thousands. In the course of the next five and twenty years it has been estimated that fully 11,000,000 have died from plague in the country. Of late years cases have been much fewer, but the disease has not died out, as it had seemed to do for fifty years prior to the beginning of this outbreak. In 1930 the return of deaths was 23,825, whereas six years earlier it was nearly fifteen times as great. Some parts of India were comparatively free and this is ascribed by Hirst to the prevalent species of flea being *Xenopsylla astia*, a much less effective carrier than the rat-flea, *X. cheopis*. We will return to this point later.

The general sanitary, or, more correctly, insanitary, conditions in the Punjab and United Provinces in the nineteenth and early twentieth centuries were conducive to spread of infection. Choksy

of Bombay in his articles on Plague in India quotes Sir J. Y. Simpson and Sir Joseph Fayrer on the physical and social conditions in England in the fourteenth century when plague was rife there and compares their account with conditions in these parts of India five and a half centuries later, described by Dr. Francis and quoted by Norman Chevers.

England in the fourteenth century.	Punjab and the United Provinces in the nineteenth and twentieth centuries.
The food consisted of salted provisions, rye bread and practically no corn. Cultivation and gardening of vegetables was not taken up till the sixteenth century. In all the towns of Europe the streets were unpaved and ill-constructed. Filth was thrown into the streets. Vaults and common sewers were non-existent, and drains ran above ground. Scavenging was imperfectly understood or neglected. The water-supply was deficient, the streets narrow, preventing free circulation of air. Internal domestic arrangements of the houses were injudiciously placed, and there was great overcrowding.	A small stone dwelling (built upon a surface thirteen feet square) consisting of two rooms each about five feet high, one above another— the upper chimneyless and practically windowless; tenanted by the entire family, often more than a dozen in number, and by the huge baskets containing the family grain ; the lower compartment (a wooden floor full of cracks, serving as media for the effluvium from below, dividing the two) being occupied by the family herds consisting of cows, goats and pigs ; a row of such dwellings (sometimes they are single or double) spread over an irregular surface, similarly tenanted and flanked at either extremity by the
The streets of London were filled with filth and garbage. The houses of the people were wooden or mud houses, small and dirty and without drainage or sanitation. The floors were of earth or clay, and were covered with rushes, straw, and other rubbish which were occasionally removed, but underneath these lay unmolested an ancient collection of beer, grease, fragments of fish, spittle, the excrement of dogs and cats and everything that was nasty. Close by the door stood the ' midden ' a collection of every abomination, streams of filth from which polluted the houses and neighbourhood, including any river at hand. People lived in a crowded state and knew little of decency, cleanliness or order. The standard of existence and morality was very low. In the fourteenth and fifteenth century soap was scarcely used at all, and it was a luxury to the labourer, who could barely afford to buy any. He lived in dirt, slept upon heaps of decayed	ancestral heap of manure, from which streamlets of liquid filth were flowing in different directions : the cottages covered with cucurbitaceous creepers : a small forest of hemp, some eight or ten feet high, luxuriating in the immediate neighbourhood of the village, a growth of underwood including nettles, etc., between the two, and more or less surrounding the latter : and an unwashed pater-familias seated in front of his fig-tree having submitted his head to be divested by a faithful spouse of the light infantry skirmishing in his unkempt hair. Conceive such a village, situated towards the base of a mountainous slope, well within the range of whatever noxious influences may emanate from the valley below ; located where there would be the veriest minimum of ventilation, and we cannot be surprised if, when sickness come, it should run rampant. The atmosphere and peculiar smell in these localities must be encoun

matter, and had no fresh vegetables to eat. Only a few cabbages could be obtained, and also onions, parsnips, carrots and some kind of beet or turnip.

Potatoes had never been heard of in the thirteenth century. Meat was scarce, and for months people consumed salted meat and fish that had suffered from keeping. There was much storage of salted food in medieval England, and in the Midlands, away from the coast, much salted fish was eaten. In fact, fish was a great article of consumption. The bacon generally was rancid and ham was alive with maggots. White bread was a great delicacy. The clothing consisted of skins and woollen stuffs.

tered to be appreciated. They are *sui generis* and very suggestive of disease.

Plague in India no longer presents the problem which it did in the earlier years of the pandemic. The following approximate figures have been given in a recent survey (League of Nations, 1937) : Between 1898 and 1918 the average yearly deaths from the disease were 500,000 ; between 1921 and 1930, 100,000 ; between 1931 and 1935 only 50,000, and its importance to the Health Department is actually less than cholera and smallpox. This reduction is ascribed, in part at least, to the establishment of some degree of immunity in the rat population which has been found to be roughly proportionate to the prevalence of plague in the areas from which the test rats were taken. Again, in India the pneumonic form is rare and the disease is essentially bubonic. Finally, sylvatic plague (see later) is a relatively unimportant problem in India ; field rats, other than the domestic species, do not exist in large numbers and ; aral plague is secondary to a *Rattus rattus* house epizootic.

Little is known concerning plague in *Ceylon* in general, somewhat more as regards Colombo. The port remained free from the disease for eighteen years after India was attacked. There was an outbreak a quarter of a century ago, recorded by W. M. Philip and L. F. Hirst. The first suspicion of its presence arose when several sudden deaths occurred in the chief grain centre of the town and were found to be due to septicæmic plague. During two years, through which the outbreak lasted, more cases were of the septicæmic than of the bubonic type and, it is worth noting, plague-infected rats did not show the usual changes although

their blood was found to contain numerous bacilli. Two hundred and two human cases were confirmed by autopsy, and of these 193 were of the septicæmic type, without any enlargement, without even any tenderness, of glands having been present during life. The symptoms were of sudden onset—tightness and oppression of the chest, and death might occur within twenty-four hours. Most of the victims were poor persons inhabiting insanitary houses, rat-infested and with earth floors. Cases were most frequent in the cooler months, December and January, when the mean temperature was just above 70° F., and less common when the temperature rose to 80° F. or over. Attempts were made to protect the contacts by inoculation of a vaccine from Bombay, but had to be abandoned as its use led to a panic and threatened to cause a labour famine.

In recent years the prevalence has not been great and there has been no epidemic outbreak. Thus in successive years from 1929 to 1935 there were respectively 41 cases, 29 deaths; 46 cases, 42 deaths; 50 cases, 48 deaths; 77 cases, 69 deaths—67 of the cases and 61 of those fatal occurring in Colombo City; 57 cases, 52 deaths, of which 30 of the cases were bubonic, 15 pneumonic and 12 septicæmic; 37 cases, 31 fatal, of which 34 cases, 30 fatal, occurred in Colombo; and 60 cases, 56 deaths, of which 42 cases were bubonic and 18 septicæmic; all but 3 of the total occurred in Colombo City.

The subject of plague in *South Africa* is too large for us to treat it in detail here; moreover, it is rather of epidemiological than of historical interest. The question will come up again when we speak of the connection between plague and rodents; here we mention a few of the salient points. In the last decade of the nineteenth century and the first four or five years of the present plague was introduced at various ports and caused extensive outbreaks among domestic rodents and not a few human cases in urban areas. Between 1903 and 1905 the ' striped mouse,' *Rhabdomys pumilio*, in the bush adjacent to some of the ports became infected and by its agency infection spread slowly during the ensuing decade and in 1914 reached the sandy inland country where gerbilles were plentiful. By their means the spread was rapid over the interior of the Union of South Africa and here and there human cases occurred. During the next twenty years human patients practically all acquired the infection by the wild, veldt, rodents; it was quite exceptional to find domestic rodents plague-infected. In 1921-2 outbreaks in the Orange River Colony and the Transvaal occurred on isolated farms and were definitely

traced to infection from gerbilles (Nachtmuis) and the multi-mammate mouse, *Mastomys coucha*, which abound in the sandy stretches of this district.   Finding of gerbilles dead in their burrows in considerable numbers led to examination of their bodies and detection in them of *P. pestis*.   They are nocturnal animals, hence the name ' Nachtmuis,' and do not enter houses, and it was the general belief that it was these animals which had been responsible for the plague in this area since 1916.

In 1934–5 the seasons for veldt rodents were favourable and the breeding of them was increased and waves of infection were observed among them and, at the same time, an increase in the number of human beings attacked and in several places domestic rodents were infected.   It is thought probable that in the near future cases of plague will again show an increase owing to the fact that the gerbille colonies have again been multiplying enormously in the neighbourhood of places where plague formerly prevailed.   *Northern Rhodesia* reported suspicious cases in 1935 in natives of the Luangwa Valley, but the suspicion was not confirmed ;   precautions were taken, however, the huts in the suspected village being destroyed and the disease, whatever it was, died out.

No cases had ever been known to occur in *Basutoland* prior to 1935, though they had been reported within a few miles of the border.   Early in January rodents were observed to be dying and examination revealed the cause to be *P. pestis*.   Rodents infest every part of the country and the danger is serious.   In May several deaths from plague were reported among natives dwelling within twelve miles of the Quthing border.   In the same year there was anxiety, and cause for it, in Bechuanaland.   In April the presence of plague was reported from Zeerust, a few miles from the border, not only among the rodents ; two human cases were notified.   Energetic measures carried out by the aid of the Health Authorities of the Union of South Africa resulted in some three months in practically freeing the Territory of rodent infection.

In certain parts of *East Africa* there has been considerable increase in cases of plague during the past decade, in Uganda in particular ;   in Kenya, and still more in Tanganyika, the numbers have shown a rapid decrease.   In *Uganda* there were 1844 reported cases in 1926 with a fatality rate of 85·3 per cent. (deaths numbered 1574) and in the following year 2171 cases, 1863 fatal, a case mortality of 86·5 per cent.   There was an extensive outbreak in the Buganda Kingdom and Eastern Province during the three

months, June–August. In 1929 the notifications amounted to 5960 and 5118 died; almost half the fatal cases (2518) were in the Mengo district. In 1930 deaths totalled 2370 among 2546 patients, and a large proportion of them were engaged in the cotton industry and were infected from the rodents on the plantations; in the following year the figures were about the same, 2378 cases, 2299 deaths. In 1932 there was an astonishing drop to 60 cases, 40 deaths, but in 1933 the numbers again rose though not nearly to so high a figure as in the preceding year; there were 858 cases, 833 deaths, a 97 per cent. fatality, nearly all in the Eastern districts where the disease had been endemic for years; there were none in the West and at Lango only in the North. The two succeeding years showed further increase in cases—977 with 937 deaths, and 2010 with 1871 deaths.

Kenya also has suffered. In 1929 Nyanza, Kikuyu and Ukamba Provinces were attacked and 763 cases were reported; in 1930 Kavirondo as well as Kikuyu had cases and 959 were notified. During the next four years the decrease was rapid, the respective returns being 604 (part a continuation of the Nairobi outbreak of the preceding year), 281 (it was said that this was an understatement, cases having escaped notification), 163 (chiefly in South Nyeri reserve of Kikuyu highlands) and 128. In the following year (1935) there was an outbreak in the Central Province; 139 notifications were received, but it was said in the report that the real number was nearer 600. In Nairobi plague seems to be associated with climatic conditions. If the rainfall is heavy, cereals are abundant, the drying of crops is delayed, prices are low and the amount of grain stored increases. The glut leads to improvidence and general prodigality and as a result the rat population rises. So outbreaks come to be associated with years of grain storage. Recent investigations have disclosed that in native reserves the rats which live chiefly in the thatched roofs of the huts and which, therefore, need not enter the hut to reach the cereal stores of the villagers harbour *X. brasiliensis* and this is probably a factor associated with the lower human mortality in plague outbreaks in native reserves as compared with that in urban areas. In townships many of the rats live in underground burrows and the prevalent flea on them is *X. cheopis*; this, the better vector, and the closer association with the human inmates account for the higher mortality of urban outbreaks.

Tanganyika has been relatively free, as compared with either Kenya or Uganda. In 1930 a few—15—cases were seen at Mbulu, Northern Province, and all were fatal; in 1931 there were 238

cases, 172 deaths ; then in successive years 12 cases (10 deaths), 9 cases (5 deaths) ; in 1934 there was none reported and in 1935 one only.

In 1928 the region of Lake Albert was found unexpectedly by a medical missionary to be a focus of plague. Further investigation confirmed this and indicated that this part of the Belgian Congo had probably been an endemic centre for thirty years or thereabouts, the infection having been introduced from Uganda.

Madagascar became infected in 1898 by the agency of a rice-steamer from India and at the present time persists with undiminished violence over the whole of the High Plateau. All three types occur, but the pneumonic is unusually common, particularly in the colder season. Epidemiologically the disease in this island is characterized by its appearing in isolated cases, peculiarly sporadic, having no obvious connection with preceding cases ; it also has definite seasonal recrudescences and occurs in small family or village outbreaks. Plague in Madagascar differs from the conditions of the disease in South Africa in that there is no evidence that wild rodents are much concerned in transmission, nor that they are reservoirs of plague. Most cases occur in the bush land of the High Plateau and the problem is a rural, not an urban one. In a very recent report of a tour made in 1937 Dr. Charles Achard states that the disease is serious, especially in the central zone. He speaks of 1363 cases of which 663 were of the bubonic type, 442 pulmonary and 258 septicæmic. Its fatality rate was very high ; 88 per cent. of the bubonic and 100 per cent. of each of the others.

West Africa suffers little from plague and there is consequently little to relate. *Nigeria* reported 188 cases, 176 fatal, in 1929 ; 65 all fatal in 1930 ; 5 all fatal in 1931 and since then none (1935). The *Gold Coast* has not reported any cases in the past decade. It is menaced, however, for the disease exists in the neighbouring administrations, at Dakar and French Senegal, and at Takoradi ships come alongside the quay. The *Gambia* also has practically a clean record. In 1930 six deaths occurred at Konti, a river port 130 miles from Bathurst. Infection was introduced from Senegal. Since then no cases have been reported. *Sierra Leone* is also free.

As regards *Australia* plague appeared at Adelaide, Melbourne and Brisbane in the opening years of the present century, but only in Sydney did it spread. Here there were 300 cases and 100 deaths. It was again introduced here in 1903, but fortunately did not spread and no epidemic resulted. Twenty years later it was once more introduced and this time the town was

less favoured and did not escape. A vessel arrived from Queensland and on it were found rats dead of plague. Soon afterwards rats on the adjacent wharf became affected, previous examination having demonstrated their freedom from plague. During the ensuing nine months thirty-five cases of human plague occurred in ten localities in Sydney and five of the secondary outbreaks were grouped around a store or stable which had obtained a supply of fodder from the wharves which had been infected at the outset.

As regards the *Western Hemisphere*. To *New York* infection was introduced in 1900, but, as in Sydney in the early years of the century, it did not extend. These towns were both favoured, for it will be remembered that the Great Plague of London was traced to two Frenchmen who died of it in Drury Lane in December 1664.

California has not suffered at all severely, but the infection has shown its presence in rodents or man since the beginning of the present century. It was introduced in 1900, probably from Hong Kong, though some think from Honolulu, and during the four following years cases of the bubonic type were seen in San Francisco, mostly in the Chinese colony. In 1907 it spread more widely over the city and in 1908 the disease was proved to exist among ground squirrels. During the ensuing decade sporadic cases were seen in six counties, but only eleven cases altogether. In 1919 pneumonic plague was reported from Oakland, thirteen cases being notified and sporadic instances were met with during the next five years. Then, that is in 1924, thirty-two cases of pneumonic plague were notified in Los Angeles and thirty of the patients died, and in addition there were five of the bubonic type, three fatal. During the next ten years only six sporadic cases of the disease were reported.

We see from the above that the last year of the nineteenth century saw plague appear in parts of the globe which, so far as is known, had never been attacked before. Cantlie writing in 1901 states :

Previous to the present pandemic plague had never appeared south of the equator ; but in Mauritius, the Cape, Madagascar, Australia and South America it has prevailed in a more or less severe form. In neither North nor South America had plague ever been known until quite recently and although in North America it is at present confined to the Chinese quarter of San Francisco, there is no guarantee of its continued limitation to that locality. The islands of the Pacific have not been exempt, the Philippines and the Sandwich Islands more especially having suffered severely.

In Great Britain plague has never obtained a footing since the Great Plague of the sixteenth [seventeenth] century until the autumn of 1900 when a limited outbreak occurred in Glasgow. Some six cases have been brought to the London docks, but no extension of the disease ensued.

In the same year deaths due to plague occurred at Oporto and Hamburg. In India the Bombay Presidency suffered more than other parts until the last quarter of 1900 when Mysore showed the greater incidence and there was a severe epidemic in Putna, Bengal.

The distribution of the disease continued to be widespread even when no serious outbreaks were taking place, and in 1925 and the following years countries invaded included Manchuria and Eastern Siberia (pneumonic type mainly), Indo-China, the East Indian islands, India, Ceylon, Iraq and other parts of south-west Asia, Northern Africa, West Africa (Nigeria), East Africa (Kenya, Uganda), South Africa, Madagascar, Sydney, California, Brazil and the Argentine.

In the French Colonial possessions in recent years, from 1928 onwards, the incidence has varied greatly, as in the British East African Colonies. In *Senegal* and *Dakar* between 1928 and 1930 there were some 2000 cases annually; in 1932 and 1933 only 200, but in 1934 another leap to 1100; 90 per cent. of the cases were bubonic, the remainder pneumonic in type. Madagascar has been referred to above in general terms; we now give a little more detail. Between 1898 and 1921 plague remained a coast disease and was bubonic in type. In 1921, however, it invaded Tamatave as bubonic, spread to Antananarivo as pneumonic and caused the deaths of forty-six persons in three months. Between 1921 and 1936 its endemicity became established and, as stated above, is present over all the High Plateau, is commonly of the pneumonic type and from time to time becomes epidemic, especially in the colder months of August and September. In French Indo-China there has been a marked decrease of cases in the last fifteen years. Thus, in 1922 there were 1300 cases reported, in 1936 only forty.

The accompanying map showing the distribution of the disease in 1934 is of interest in demonstrating that many areas which had suffered severely, particularly Great Britain, Europe and the Mediterranean, were free of infection and others, such as Libya, Egypt and Syria, which in times gone by were the main foci of dissemination, showed but little. It is seen, however, that active foci are many and widely distributed: India, Ceylon, Burma,
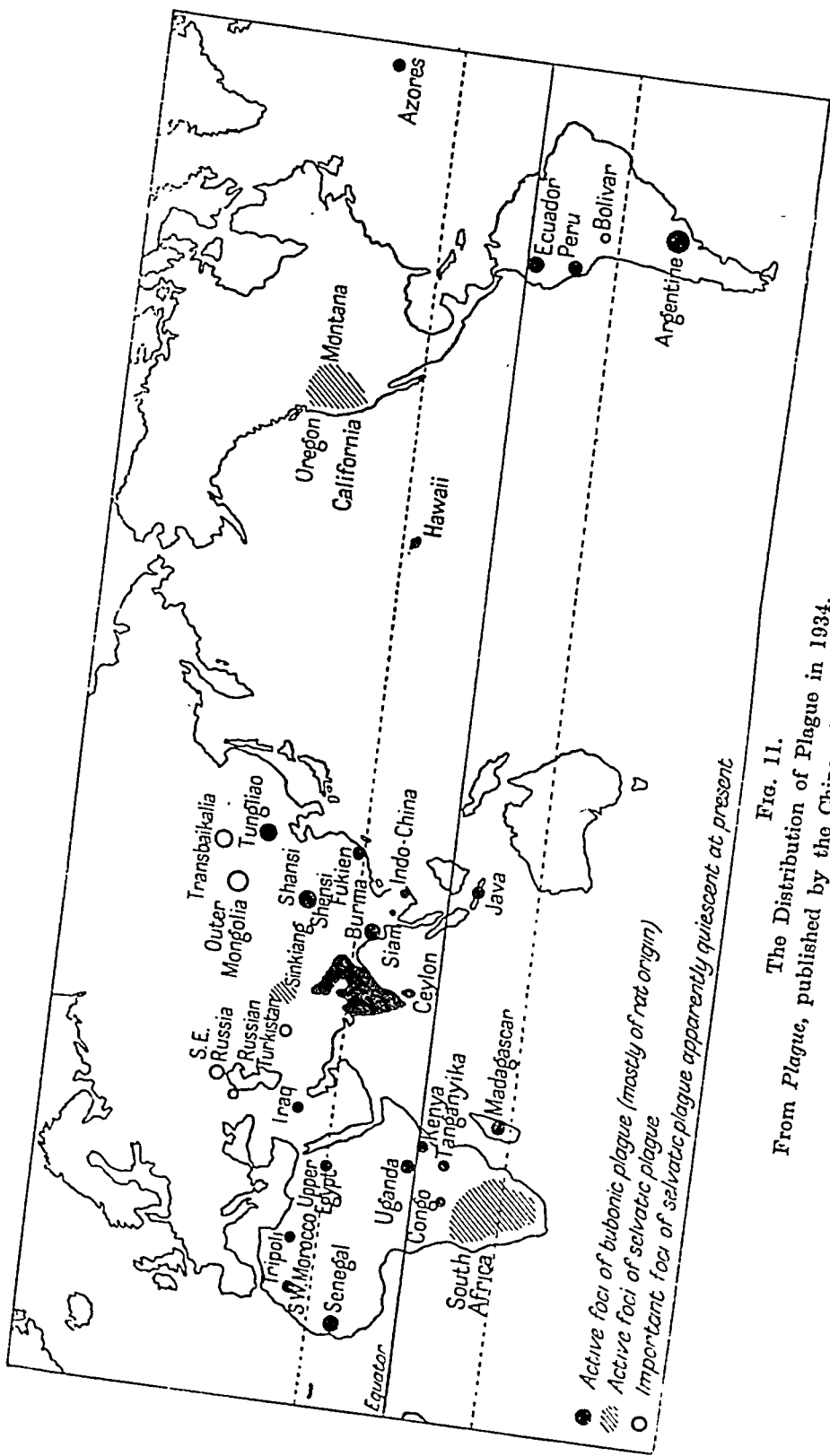
Fig. 11.

The Distribution of Plague in 1934.

From *Plague*, published by the Chinese National Quarantine Service.

Siam, Indo-China, Java (where in 1934 there was a serious epidemic, particularly in the West; here 20,569 cases were recorded, in Central Java 2668, but in East Java only two), China (Fukien, Shansi, Shensi, Tungliao), Hawaii,. Ecuador, Peru, Bolivia, the Argentine, the Azores, Tripoli, Morocco (especially the south-west), Senegal, Upper Egypt, Uganda, Kenya, the Congo, Madagascar and South Africa.

As standards of living improve and the knowledge which we have is applied it is not unreasonable to predict that these places also will in time become unfavourable for the spread of plague.

3. Types

Till we come to comparatively recent times there were only two main types of plague recognized, the explosive and the bubonic. The former applied to those patients dying in 48–72 hours in a state of intense toxæmia—that is, septicæmic plague—before buboes had had time to develop. The latter was more obvious, but cases might be mild or severe. Though in the older records we find hæmorrhage mentioned, from nose, lungs, stomach and bowel, these were looked upon as rare accidental symptoms. Modern opinion as to the origin of pneumonic plague does not differ very much from this in maintaining that in the course of bubonic plague the lungs become the chief seat of infection and, the bacteria being scattered by cough, attendants or associates may be attacked without the intervention of the insect vector, and hence the greater infectivity of the pneumonic patient. Descriptions of the Black Death tell us that hæmoptysis was a common symptom and this readily accounts for the high morbidity and fatality rates.

Coming to our own times we can all call to mind the pandemic of influenza of 1918 when the bloody sputum and high fatality rate led to the conjecture, the suggestion, the scare that we were faced, not merely with influenza but with another pandemic of plague. So common indeed was this hæmoptysis in the Black Death that it came to be looked upon as a *signum pathognomonicum*. Thus, at Avignon for the first two months of the epidemic the main symptoms were fever and spitting of blood, ending fatally in two or three days; after this cases appeared in ever-increasing proportion with " boils and sloughs," that is, buboes in axilla and groin, the patients succumbing in five days or more.

In the outbreak in India in 1820 two forms were recognized; in one the symptoms were severe pain in the head, back and limbs, marked thirst, delirium and presence of hard very painful

swellings of the axillary or inguinal glands ; in the other high fever, with pain, especially in the chest, delirium, coughing up of blood in quantity, progressive dyspnœa and death in forty-eight hours or so. In the Pali plague sixteen years later the same two types were observed side by side, and Webb wrote : " The Pali plague exactly resembles the great plague, the Black Death."

Hirsch was far-seeing and astute in calling the Indian plague only a " modification " of the bubonic plague. He states :

The complication of bubo-plague with bleeding from the lungs has occurred in many other epidemics of plague, and the Black Death and the India plagues differ from these only in so far as the complication, for reasons that we do not know, was much more frequent, amounting to a *signum pathognomonicum*, and accounting for the extraordinary malignancy of those epidemics.

The pneumonic type is generally, though not essentially nor always, a disease of cold climates. The Black Death, as Professor Greenwood has pointed out, showed evidence of change of type with change of seasons. In the winter of 1347 at Avignon it was of the pneumonic type ; in the summer of 1348 at Weymouth it was prevailingly bubonic ; in the spring of 1349 in London again pneumonic and later in the year in the east of England bubonic.

This, however, does not always hold good. In an outbreak of limited extent in the Gold Coast in 1908 cases of bubonic and pneumonic plague existed side by side ; 134 of the latter were recorded and the bubonic were in larger numbers. In Kashmir the same year 1400 cases of the pneumonic form were recorded. India, Hong Kong, Yunnan, Canton and Kirghiz are acknowledged endemic centres of bubonic plague, and though cases of secondary involvement of the lungs are far from rare there is no record of serious epidemic pneumonic plague in them. The pneumonic form is not absent from Kwangsi, Kwangtung and Fukien, but cases are usually restricted to isolated areas or to small groups in epidemics of the bubonic form.

In Siberia and Mongolia, on the other hand, curious alternations have been observed. Thus, in 1905 bubonic cases were seen on the Russo-Manchurian frontier ; in the following year the pneumonic type occurred at Atagaitin in Siberia and in 1908 the same in North-west Mongolia. In the severe epidemic of 1910 there were a few pneumonic cases at Daurija in Siberia, 400 in Manchuli town, but in the Manchurian outbreak 60,000 died. In 1911 there were five bubonic cases at Sharasone (Siberia) and in 1912 three pneumonic cases at Chita.

At the beginning of the century cases were divided into a

much larger number of types. As we have seen, in the early days there were two—the toxic (or septicæmic as we would now designate them) and the bubonic (some of which might be mild, some severe, some with hæmorrhages). Later, as epidemics of the pulmonary form were seen while bubonic might be few, a third type, the pneumonic, was added. But in 1899–1900 a more detailed classification was made, based largely on prominent clinical signs, into bubonic, intestinal, pneumonic, convulsive, toxic, typhus-like, ambulatory, sidereal and pestis minor. This last was a term introduced by Cantlie as a synonym of climatic bubo, not for mild bubonic plague. We now know that climatic bubo is a venereal disease, lymphogranuloma inguinale, having nothing to do with plague. Cantlie, however, was strongly of opinion that it was an indolent, chronic form of plague and thought he had found support for his opinion when Rife reported in 1902 fifteen cases on a ship cruising in the Caroline Islands. It is true that all the patients had ulcers or abrasions on the legs, but Cantlie thought this obvious explanation was outweighed by the unlikelihood of fifteen persons with wounds " developing inguinal buboes simultaneously " and he maintained that they were due to some common infection—attenuated plague.

The term *pestis minor* is nowadays applied to a mild form, ambulatory plague, in which there is fever, a bubo which suppurates and is followed by a speedy recovery. We have now returned to the simpler classification into bubonic, pneumonic and septicæmic.

4. THE CAUSE

We have seen in the foregoing that *climate* and *season* seemed to play some part in determining the type of the disease, but in spite of the knowledge of pandemics in the past, there was a widely held belief that plague ceased at the tropical zone. The statement was made that though plague had been known to exist, for example, in Lower and Middle Egypt for centuries it did not penetrate Nubia or Abyssinia or the tropical parts of Egypt. Further investigation led to the conclusion that epidemicity was favoured by temperature moderately high, but was checked by extremes, whether of heat or cold. The latest authority to ascribe some influence at least to climate is Sir Leonard Rogers who has made an intensive study of this question and its application to disease. He came to the conclusion that plague is reduced by high temperature and high " saturation deficiency " (that is, the difference between the actual tension of aqueous vapour present in the atmosphere at the temperature in question and the tension

of aqueous vapour that would be present in a saturated atmosphere at the same temperature). Saturation deficiency is, then, a measure of the drying capacity of the air (which, to anticipate, is inimical to fleas). So, states Rogers, decline of plague in India during the height of the hot season is due to high temperature and saturation deficiency. By studying these factors over a number of years Rogers was able to forecast the probable rise or fall of plague.

Race was held to play some part, and it was held that blacks were the most susceptible and, after them, in order, Berbers, Nubians, Arabs, Turks, Greeks, Armenians, and, last and least, Europeans. We now believe that the reason is not racial but social.

When it was observed that outbreaks might originate at a height, in mountainous districts on dry and non-alluvial soil, as well as on the low damp plains, it was argued that it was not the characters of soil or climate *per se* that fostered plague and its extension, but associated hygienic deficiencies, for in all epidemics studied it was noted that conditions of mal-hygiene prevailed—overcrowding, inadequate ventilation, accumulation of filth in houses and streets, defective disposal of excreta, human and animal. In ascribing the disease to these conditions, writers of the time were merely voicing the general opinion that disease was generated by dirt. They seemed to overlook, at least to disregard, the fact that equally bad social and hygienic conditions might exist without any outbreak of disease. It was not until later when the *rôle* of rats in the epidemiology of plague was determined that it was shown that insanitary conditions, apart from favouring rats and their multiplication, played no active part. In Egypt, Syria, Asia Minor, Turkey, India, Mesopotamia, Persia, wherever plague was rife, misery, poverty, slums and general insanitation were present. There is no need to amplify this ; one example will suffice. Rennie, describing conditions in Gharwal where plague was severe, wrote :

The filth is everywhere—in their villages, their houses and their persons. . . . Their dwellings are generally low and ill-ventilated except through their bad construction, and the advantage to the natives in other parts of India of living in the open air is lost to the villagers of Gharwal, from the necessity of their crowding together for mutual warmth and shelter against the inclemency of the weather.

Again, it has been said of the Gharwal native that he rarely washes ; he wears his clothing until it drops off ; he lives in a small, overcrowded, almost hermetically sealed hut of two compartments, the lower being occupied by the cattle, and the upper by the

family (sometimes as many as thirteen persons), all available spaces being taken up by the baskets of grain, and the only hole in the wall is stuffed up with straw; old heaps of manure surround the house; the hemp and other growths rising to eight to twelve feet impede the circulation of air in the village.

More recently in 1876 in Iraq-Arabi, Hillah—a filthy town crowded with a destitute proletariat—was decimated, whereas Kerbela, a town clean and prosperous, was almost entirely spared. In Baghdad it was said " the poor were seldom spared, the wealthy hardly ever attacked."

So it came to be believed that the cause was uncleanliness, aided by overcrowding and famine, " thus resembling typhus," and the conditions favouring spread were summed up as warm humid air, low, badly-ventilated and crowded dwellings, accumulations of putrefying animal and vegetable matter in the vicinity of the dwelling and the close contact between people, cattle and grain. We have noted above how dirt had been considered by Homer to be a potent cause of plague, its presence offending Apollo.

About a hundred years ago there was in vogue an idea that plague arose from *cadaveric poison* and this conjecture was thought to have gained real scientific support when two Frenchmen, Lagasquie and Pariset, sent to Egypt in 1828 to study the disease, published nine years later a report " On the Causes of Plague." It is worth quoting as one of the finest examples of the *post ergo propter* fallacy in our knowledge. They showed by a study of history from the time of Herodotus to that of the epidemic they were investigating, that plague made its first appearance in Egypt in A.D. 543, that this was the time when embalming gave place to burial in deference to the spirit of Christianity. Burial in Egypt was not deep and the atmosphere became heavily tainted with the products of cadaveric decomposition. The argument ends in these words :

> Thus it happened that with this most dangerous innovation a most dangerous disease was created. So long as corpses were embalmed there was no plague ; when that practice ceased pestilence appeared. Is there a more conclusive or more notable piece of evidence in any science in which the facts are not ascertainable with mathematical certainty ?

This was countered by the statement that in war armies camp on battle-fields where the air is heavily charged with the products of decomposition from the bodies of men and animals buried in numbers in shallow trenches ; that people in besieged towns suffer

for months from fatal epidemics of typhus, dysentery and the like, but neither in the field in the former case nor in the town in the latter does an outbreak of plague arise. It was argued, therefore, that, whatever the general conditions, there must be present or introduced the " specific virus of plague," or, as some believed, there might possibly be a transmutation of one disease—malaria, typhus, or some other—to plague.

Others made the vague, and in those days incontrovertible, suggestion that under the above conditions plague arose from an " emanation out of the earth " or an " emanation from the sky." Egerdes early in the eighteenth century sagely surmised that transference occurred by introduction of the poison by persons affected or by goods, or by *fomites*, as by a tinder from place to place, and consequently, he concluded, the plague virus must be an organized poison.

This idea of transmutation was perhaps not quite so fantastic as it appears to us at the present day, for plague would occur in a malarious district—Wallachia, for example—and the two diseases would exist side by side ; one person in a house might suffer from malaria, another contract plague, a third might get both. Seidlitz is largely responsible for the spread of this doctrine. He says :

> The fever of the plague transplanted from its native soil and divorced from the epidemic constitution favourable to it, changed into an intermittent. Why, then, should not intermittent fever, reversing the order, pass into bubo plague, when circumstances and epidemic constitution are auspicious ?

J. B. Goiffon, a physician of Lyons, in 1720 enunciated a vague idea or forerunner of the microbic theory of plague when he stated that the only satisfactory explanation of the evolution and propagation of plague was the existence of certain *insectes volants* invisible to the eye.

The conception that there must be some " specific virus of plague " soon led to the further question, What becomes of this virus between the outbreaks ? For if the disease starts up again after an interval, it may be short or long, there must be some method of maintaining it. The second of these could not be answered until the first had been solved and this was accomplished by Yersin's discovery of the causative organism, now known as *Pasteurella pestis*, in Hong Kong in 1894. It is a matter for regret that in a British colony where the disease was rife and opportunities consequently abundant the discovery should have been made by a Japanese. Yersin's name is often coupled with

that of another Japanese, Kitasato, but on insufficient grounds. It is true that on 7th July, 1894, Kitasato announced the finding of an organism in plague cases, but this he described as Gram-positive and slightly motile. He probably mistook some contaminant for the causative organism, which is neither Gram-positive nor motile. On the 30th of the same month Yersin isolated the true bacterium, and under considerable difficulty since, not permitted to perform autopsies, he isolated it from excised buboes ; with this bacterium he carried out animal experiments before publishing his account of the organism, as a small ovoid bacterium, pleomorphic on culture, non-motile, non-sporing, Gram-negative, and showing bipolar staining. From an epidemiological point of view it is interesting to note that it has but weak powers of resistance and is, therefore, not adapted to saprophytic life (but see below). Though clothes, etc., may remain for a time infected, their infectivity and so their likelihood of bringing about spread of the virus is remote. When freshly isolated or, still more, when the organisms gain entrance through a wound, as when an autopsy is performed, the infectivity is very great and several instances of this and of laboratory infection have been recorded in Tokyo, Chita, Leningrad, Berlin and Vienna. Also a fresh culture has been utilized for homicidal purposes—in the Bhatacharya-Pandey case (1933) reported by the Director of the Haffkine Institute, Bombay, and under the title The Pakur Murder, by Captain D. P. Lambert, I.M.S. (Medico-Legal Review, 1937, p. 297).

Recent experiments have shown that plague bacilli can be incorporated in tear gas or asphyxiant gas without losing virulence ; they could thus, theoretically, give rise to plague pneumonia by inhalation or the bubonic form by wound inoculation under modern methods of warfare on the Continent.

The Pasteurella (Bacillus) pseudotuberculosis rodentium, first seen by Malassiez and Vignal in 1883 and named by Pfeiffer in 1889 (Topley and Wilson) some years before Yersin's discovery of the plague bacillus, is found in rodents and strongly resembles the P. pestis ; in fact the differential characters are in the main quantitative and diagnosis of one from the other is difficult. The former is more of a saprophyte. Bessonova, Lenskaya and their co-workers have recently (1937) reported that during the preceding seven years out of 214 strains of the plague organism five have undergone spontaneous transmutation to P. pseudotuberculosis rodentium and come to differ entirely from S and R variants of P. pestis. The reverse, fortunately, does not seem to occur ;

the transmuted strains have remained stable for periods up to seven years.

5. TRANSMISSION

(i) *The Rodent*

In the apt words of Professor Greenwood, plague is a good, perhaps the best, example of the belief of unlearned people containing more essential truth and practical wisdom than the opinions of wise and learned men. Himalayan villagers have long believed that unusual death among the rats preceded outbreaks of plague, and centuries earlier still, in the days of the Israelite-Philistine controversies, we find recorded the offering of " images of your emerods (swellings) and images of your mice that mar the land " after capture of the ark by the Philistines (See Greenwood's *Epidemics and Crowd Diseases*).

More than 150 years ago a Chinese named Shih Taonan, who lived from 1765 to 1792 and himself died of plague, wrote a poem entitled Tim Yü Chi in which the following occurs (the translation is by Dr. Wu Lien Teh and is given in his work on Plague) :

> Dead rats in the east,
> Dead rats in the west !
>
> .   .   .   .   .   .
>
> Few days following death of the rats,
> Men pass away like falling walls !
>
> Deaths in the day are numberless,
> The hazy sun is covered by sombre clouds.
>
> While three men are walking together
> Two drop dead within ten steps !
>
> People die in the night
> Nobody dares weep over the dead !
>
> The coming of the devil of plague
> Suddenly makes the lamp dim,
> Then it is blown out,
> Leaving man, ghost and corpse in the dark room.
>
> The land is filled with human bones,
> There in the fields are crops,
> To be reaped by none ;
> And the officials collect no tax !

Immediately preceding the outbreak which followed the Taiping rebellion dead rats in large numbers had been found in the walls and ceilings of the dwellings.

The actual part played by the rat was, of course, not known till much later when the Indian Plague Commission issued their

report in 1906. An earlier notion was that plague was due to a poison in the damp air of the soil and as rats lived underground they were the first to contract the disease. The bodies of the rats dying from it putrefied and poisoned the air, which, being inhaled by man, set up the disease in him. Hence, to prevent infection what was needed was cleanliness, ventilation and careful avoidance of damp, dark places, looking out for dead rats and those who buried them were advised to plug their nostrils and turn away their faces to avoid inhaling the gases of putrefaction.

The Russian explorer, Prjevalski, who was in Shensi Province in 1870–3, was told by the inhabitants of an infectious disease among the marmots there which sometimes was transmitted to human beings. In Mongolia also the natives were aware of the connection between plague and rodents ; they had a wholesome dread of dead tarabagans and of localities where these were found in any numbers (see p. 712, *supra*). When human cases occurred discretion would often overcome their humanity or valour, and relatives and neighbours would run away leaving the victim to his fate. In this district all human outbreaks of which detailed information is obtainable seem to be traceable to the tarabagan. These animals stay above ground between April and September, hibernating in the cold season, and usually live well away from human dwellings. Hence plague is a disease of late summer or autumn in these localities when the inhabitants camp in the fields for hay-harvest and for the hunting of these animals.

In the year 1894, that noteworthy for the discovery of the organism of plague, there was a very fatal epidemic in Canton, already mentioned (p. 712, above) and there is no doubt that the Chinese at that time were well aware of a connection between mortality in rats and plague in man, for one Chinese official offered a reward of 10 cash for every dead rat brought to him and in a month they amounted to more than 35,000. Dr. Rennie dissected many of them and found enlarged glands in 90 per cent. and basal pulmonary congestion in 40 per cent. and he asked : " Is the disease in man and animals identical ? Should bacteriological examination give an answer in the affirmative, then we must recognize that these rodents are active agents in transmitting the disease from place to place for long distances overland." This, we now know, does not necessarily follow, and migration of rats ' for long distances ' is disputed by many authorities. Nevertheless, the observation was a shrewd one, for at that time the majority of medical men did not support the rat theory ; thus J. A. Lowson in the official report of the Hong Kong outbreak

of the same year (1894) wrote : " The question of the infection of rats previous to the epidemic being noted in human beings has been made too much of." Simond in 1898 noted the frequency with which those who handled recently dead rats caught the disease, but remarked that this did not occur if the rat had been dead for twenty-four hours or more. He thought that the number of cases contracted by direct human contact was insignificant compared with those acquired from the rat.

Year by year the belief in rats as vectors gained in strength. In 1901 Ashburton Thompson of Sydney expressed his opinion that they played the chief part ; others went farther and said that plague was primarily a disease of rats and that human infection was only occasional or an accidental occurrence. In 1903, though rats and plague were known to be somehow connected, the part played by their ectoparasites was not known, and an anti-plague experiment carried out at San Francisco is therefore of interest. The Federal Health Officer set out to test the theory by basing his anti-plague measures upon rodent eradication or eviction, and this may be regarded as the *origin of rat-proofing as a control measure*. Whites and Chinese lived together in crowded quarters overrun by rats and the City Authorities and Mercantile Associations resolved on rat destruction and rat exclusion by rendering the houses rat-proof. In February 1905 we read : " No plague infection has been observed for fourteen months," nor was there any till two years later, twelve months after the disastrous earthquake and fire, when refugees were many and quarters few and the people had to be crowded into cottages which afforded good harbourage for rats. An epizootic occurred, accompanied and followed by an epidemic. The outbreak was cut short by demolishing the cottages.

In 1904 Gordon Tucker (*Indian Medical Gazette*) propounded a different view, the opposite of that previously held, namely that rats are infected by man and not man by rats primarily, and he stated that the view of an epizootic in rats being the cause of an epidemic among human beings was a " pernicious theory." Incidentally we may mention here that in his opinion the rat-flea had no concern in the transmission of plague, the disease being a soil infection. This theory was demolished when the British Plague Commission in India issued their report in 1906.

In the Manchurian epidemic of pneumonic plague in 1910, already referred to, the disease originated with the Mongolian

marmot or tarabagan which infected inexperienced hunters and skinners. Then, by overcrowding in insanitary dwellings case to case infection of the pneumonic type led to the death of 42,302 persons. Speaking of the tarabagan, *Arctomys bobac*, Dr. Wu Lien Teh states that it is never affected in the form of an extensive epizootic and that, though it occasionally suffers from plague, it plays a small part in comparison with that of rats.

In California the chief transmitter is the ground squirrel, *Citellus beechyi*. McCoy in 1911, giving the history of eleven human cases, found in six axillary buboes and a clear history of handling these animals shortly before symptoms appeared.

Dr. J. Harvey Pirie in the course of his investigations (1927–8) on the bacteriology of plague and its occurrence in wild rodents of South Africa reported eleven different species naturally infected. The commonest is probably the gerbille, *Taterona (Tatera) lobengulæ*.

Here may be a fit place to mention a point not sufficiently realized, that rats found dead, though showing none of the usual plague lesions, may harbour *P. pestis* in virulent form. In this connection two points call for emphasis : first, that plague must be suspected when rats are found dying or dead in unusual numbers, whether or not they show the macroscopic changes regarded as characteristic ; second, that rats are infected with bipolar-staining organisms other than that of plague and that such organisms when isolated should always be checked by experimental inoculation. As a concrete example of this may be instanced the mortality among field rodents in and about De Aar in 1927, believed at first to be due to plague. Investigation showed this to be erroneous ; though the disease was transmissible by inoculation or scarification in Namaqua gerbilles from infected to healthy and an organism can be isolated which is fatal to gerbilles, it is certainly not *P. pestis*.

There is no need to stress the fact that human outbreaks are often preceded by epizootics. Mention has been made of the Manchurian epidemic of 1910 ; again, the Narinsk epidemic of 1929–30 was preceded by an epizootic among tarabagans, *Arctomys centralis* and other species, and in the Verni district by an epizootic among the local hares. Rats and other rodents do not migrate to any distance and carry plague to outlying districts ; probably the plague-infected rat is too sick to travel more than a short distance. Importation to a fresh locality at a distance cannot as a rule, perhaps never, be laid to the score of rodents, but to man or to insects carried in merchandise. The rat burrow is

an ideal spot for plague development. Investigations carried out in Madras in 1933 showed that though the external temperature might range over 20° F. or more, 86·5° to 63°, that within the burrows varied only between 72° and 79° F. ; further, a fairly uniform high degree of humidity is maintained, though that outside varied widely. In other words " the rat-burrow provides optimum facilities for plague infection in fleas to tide over the unfavourable hot months."

The association of rodents and plague is now so generally a matter of everyday knowledge that we are inclined to forget those whose work has given us that knowledge. It is but right that they should be remembered and the chief of them were Lowry at Pakhoi who worked at the subject in 1882, and Rennie at Canton in 1894, the same year that Yersin discovered the bacillus in rats and man in Hong Kong. In 1897 Ogata, working in Formosa, showed that within 24–48 hours after death rats were free from ectoparasites and could be handled with impunity, and he was thus led to a study of the rat-flea as the actual vector. In 1897 also Roux and Yersin stressed the connection between rats and plague and urged destruction of rats as a prophylactic measure ; they were supported by Simond and Hankin. Ashburton Thompson at Sydney in 1900 and Blackmore at Port Elizabeth in 1902 added to our knowledge of the relation between epizootics in rats and plague in man, while in 1904 Liston in Bombay showed that *R. rattus* and *R. norvegicus* did not play equal parts in plague transmission ; in fact, our present immunity from plague in Great Britain is due, not solely to modern methods of quarantine and inspection of immigrants, but in part, and perhaps in great part, to the facts that the black or house rat was in the seventeenth and eighteenth centuries displaced by the brown or sewer rat which does not breed inside the house, and also that the wood and plaster house was replaced by the cleaner brick and stone structures in which rats would not nest.

In 1905 Liston, Lamb, Petrie, Rowland and the members of the Indian Plague Commission in general clarified the whole problem, showing that contact with the rat was not followed by plague if fleas were excluded, that healthy rats could be kept in contact with live plague rats and with rats dead of plague without contracting the infection and that the disease was not acquired by ingestion.

The number of rodents now definitely known to suffer from spontaneous plague is great and it may be of historical interest

to note when and where the more important of these were proved.

Date.	Name of Rodent.	Locality.
1895	*Arctomys bobac* (Tarabagan)	Transbaikalia and Mongolia.
1898	*Sciurus palmarum* (Squirrel)	India.
	Hydrochœrus capybara (Porcupine) . . .	Mysore, India.
1902	*Cavia cobaya* (Guineapig).	Sydney.
1906	*Rhabdomys pumilio* (Striped mouse) . .	South Africa.
	Gunomys bengalensis (Mole rat)	India.
1908	*Citellus beechyi* (Californian ground squirrel)	California.
	Cricetomys gambianus (Hamster rat) . .	Gold Coast.
1910	*Bandicota indica* (Bandicoot)	India.
	Neotoma fuscipes (Dusky-footed wood rat).	California.
1911	*Lepus europœus* (Hare)	England.
1913	*Citellus pygmœus* (Small suslik)	South-east Russia.
	Pelomys fallax iridescens	East Africa.
1915	*Bandicota malabarica*	India.
	Microtus arvalis (Field mouse) . . .	South-east Russia.
1917	*Citellus fulvus* (Large suslik)	South-east Russia.
	Microtus socialis (Field mouse) . . .	South-east Russia.
1919	*Xerus erythropus* (Palm rat)	Senegal.
1920	*Hesperomys palustris* (Field rat) . . .	New Orleans.
1921	*Mastomys coucha* (Multimammate mouse) .	South Africa.
	Tatera lobengulœ (Gerbille)	South Africa.
1922	*Funambulus palmarum* (Squirrel) . . .	Ceylon.
1923	*Arvicanthus niloticus* (Field rat) . . .	Egypt.
1924	*Geosciurus capensis* (Ground squirrel) .	South Africa.
	Rhombomys opimus (Sand mouse) . . .	Turkestan.
	Paratomys luteolus (Eastern Karoo rat) .	South Africa.
	Malacothrix typicus (Large-eared mouse) .	South Africa.
	Cavia aperea (Cui)	Argentine.
	Pedetes caffer (Spring hare)	South Africa.
1925	*Arvicanthus abyssinicus nubilans* . . .	East Africa.
1926	*Desmodillus auricularis* (Namaqua gerbille)	South Africa.
	Cricetus cricetus (Hamster)	South-east Russia.
	Alactaga elater (Small jerboa) . . .	South-east Russia.
1927	*Mystromys albicaudatus* (White-tailed rat) .	South Africa.
	Gerbillus tamaricinus	South-east Russia.
	Lagurus lagurus (Vole)	South-east Russia.
	Myotomys broomi (Broom's Karoo rat) . .	South Africa.
	Lepus timidus (Hare)	Transcaspia.
1928	*Spermophilus dauricus* (Dauria sisel) . .	Transbaikalia.
1929	*Gunomys gracilis*	Ceylon.
	Microtus Brandti	Transbaikalia
	Myotomys unisulcatus (Cuvier's Karoo rat)	South Africa.
1930	*Arctomys caudatus* (Marmot)	Southern Kirghisia.
	Arvicanthius rufinus	Senegal.
1931	*Ellobius talpinus*	South-east Russia.
1933	*Legada deserti* (Dwarf mouse) . . .	South Africa.
1934	*Funambulus sp.* (Squirrel)	South India.
	Golunda ellioti	South India.

Date.	Name of Rodent.	Locality.
1934	*Brachytarsomys albicaudata*	Madagascar.
1935	*Dipus sagitta* (Jerboa)	South-east Africa.
	Citellus columbianus (Columbia squirrel) .	Oregon.
	Peromyscus truei gilberti (Gilbert white-footed mouse)	California.
	Neotoma cinerea occidentalis (Western bushy-tailed wood rat)	California.
	Neotoma lepida intermedia (Intermediate wood rat)	California.

We may briefly sum up by saying that rodents capable of transmitting infection through their ectoparasites are many. In England, the rat, and in particular the black rat because of its closer association with man than the brown or grey rat. In Africa, *Psammomys rondairei, Dipodillus dodsoni, D. campestris, Gerbillus hirtipes, Meriones shawi* in the northern districts ; *Tatera (Taterona) lobengulæ, Rhabdomys pumilio, Mastomys coucha* in South Africa. In California, *Xerus erythropus, Arvicanthus rufinus, Citellus beechyi* ; in Russia the suslik, *C. pygmaeus, Pallasiomys meritianus, Arctomys bobac,* and probably others in China.

Dr. Wu Lien Teh gives a list of seventy-two rodents other than domestic rats and mice which are known to suffer from plague in nature ; also another fourteen suspected and thirty-six in which natural plague has not been found but which are susceptible to artificial infection.

In South Africa the infection seems to persist, smouldering as it were, among wild rodents even when these are not numerous, and in the warm weather it may flare up and extend rapidly and widely. Some think that the gerbilles migrate and carry it over a wide area, but this is doubted by Wu Lien Teh (see above, pp. 732, 734).

Transference of infection from wild to domestic species of rodents is of interest. In Belgium and other parts of the Presidency the bandicoot disappeared from the houses with the advent of plague. It probably suffered heavily for there was no evidence of its migrating. At the Calcutta Conference in 1934 it was held that epizootics in the Cumbum Valley were often heralded by death of bandicoots (Peramelidæ) followed by high mortality among rats and mice. Also in Dakar, French West Africa, *Mastomys coucha* seems to play the part of intermediary between wild and domestic rodent infection.

(ii) The Insect

We have seen how widespread was the belief in rodents, especially rats, as the source of human plague for many years, in some parts even centuries, but this, though of fundamental importance, gave rise to more problems than it solved. Three in particular: First, How did the infection pass from rat to man? Secondly, How do rats pass the infection among themselves? Thirdly, When evidence incriminating the flea accumulated, Why was not man to man transmission more common, for it had been recognized that, if the lungs did not become involved, the bubonic plague patient constituted but a little danger for his associates?

The history of the investigations to answer these questions is of considerable interest and may be said to start in 1897 when Ogata began to study the problem. He found that some hours after the death of a rat from plague, when the body is cold, it can be handled without risk and he noted that whereas at the time of death the body is infested with parasites, later there are none—in other words, as the body cools the ectoparasites leave it. Ogata argued that the actual transmitting agent might be one of these parasites and most probably, being most numerous, the flea.

To test his surmise he crushed fleas taken from a plague rat and injected an emulsion of them into mice and thereby set up the disease. Further, it was obvious that the fleas had become infective by sucking the blood of the rat, and hence it followed that in the rat plague was, at some period at least, a septicæmia.

This was confirmed in 1898 by Simond in Bombay, who similarly produced plague in mice by inoculating them with an extract of crushed fleas taken from a plague rat, and shortly afterwards Ashburton Thompson of Sydney supported the rat-flea theory on epidemiological grounds.

Next came Tidswell who in 1900 found the plague bacteria in the stomachs of fleas which had been allowed to feed on infected rats and in 1902–03 Gautier and Raybaud at Marseilles infected rats experimentally by allowing fleas which had fed on plague rats to bite the healthy animals. Further confirmation followed, notably by Verjbitzki in 1904 and Ashburton Thompson in 1906. Hitherto, even when it was known that plague bacilli could be found in the intestine of fleas fed on plague rats, opinion was by no means unanimous that healthy rats became infected by their agency; healthy rats were thought by some to acquire infection

by eating dead rats. Objections to the rat-flea infection of man were in the main two : First, that it was frequently observed that fleas found on rats will not bite man ; second, in hospitals where plague patients were treated the sick and the healthy are often bitten by fleas and other insects, but instances of transmission of the disease from the sick to the healthy are so rare as to be negligible (except in those with pulmonary complications when infection may be direct without any insect-intervention). Others, again (e.g. White, in the *Medical Record*, 1905) stressed infection not so much by bite as by contact or dejecta—and experiment showed that crushed fleas were infective.

The idea that rats acquired the disease by feeding on others dead of plague was developed into a theory, in 1905, that man also might become infected by food, and one author went to the extreme in stating his belief that human infection was mainly alimentary.

In the meantime Glen Liston, working at the Bombay Plague Laboratory, proved once again, in 1905, that infected fleas left the dead rat as the body cooled, and he showed further that though the rat flea, *Xenopsylla cheopis*, prefers rat to man, nevertheless if, on leaving the dead rat it fails to find another rodent host, it will have no hesitation in attacking man. He found the common Indian rat-fleas, *X. cheopis*, on human beings in plague-infected houses.

It remained for the English Plague Commission working in Bombay to establish in 1905–06 on definite experimental evidence that *X. cheopis* is the transmitter of plague from rat to rat, thus confirming the report of Gautier and Raybaud's work in Marseilles.

The Commission used special cages with muslin lining to prevent escape of fleas and so constructed that healthy rats could not come into direct contact with diseased rats or their excreta. They also determined the height to which fleas could jump and showed that healthy animals within jumping distance of the fleas of an infected animal caught plague, while others at a greater distance escaped. Confirmatory evidence was obtained by observing the relation of the primary bubo to the site of the bite.

They showed also that fleas became 'blocked' by growth of ingested bacilli. The blood of a rat shortly before death from plague may contain up to 10,000,000 bacilli per c.c. and the capacity of the stomach of a *X. cheopis* is 0·5 cmm., so a single flea can imbibe up to 5000 plague bacilli. In time these would be found massed in the stomach like a distended culture tube

and the organisms, when passed in the fæces, were still virulent. The fleas might remain infective up to twenty days after removal from the dead host, or experimentally in moist atmosphere and a temperature between 50° and 59° F. more than twice as long, even up to fifty days, and at 80° F. up to twenty-three days.

Anticipating the chronological order of events, we may add here that in 1914 Bacot and Martin showed that the bacilli multiply in the stomach of the flea and fill it and the proventriculus which becomes so plugged—' blocked '—that its valvular action cannot be performed and the lumen is obliterated. On the insect attempting to feed, the blood and culture distend the œsophagus and the organisms are driven back, regurgitated, by elastic recoil of the walls of the pharynx and the œsophagus when attempts at sucking cease.

The Commission showed also that infected fleas could be conveyed in clothing, in grain and gunny bags and in cotton, and remain infective for various lengths of time.

The findings of the Plague Research Commission cannot be recorded here in detail. They considered four factors regarding seasonal prevalence, namely climate, variations in virulence of the bacillus, variations in the number of rats and the proportion of immunes to susceptibles, and the variations in the number of fleas. They concluded that the rise of an epizootic and consequently the risk at least, if not the actual occurrence, of an epidemic depended upon a suitable mean temperature, between 50° and 80° F., a sufficient number of susceptible rats, and of rat-fleas.

By this time, 1906, we may say that the following summarizes the facts known :

1. Plague infection can be carried by fleas from an infected to a healthy rat.

2. The flea can retain the bacillus alive and virulent for periods up to two to three weeks. [But Dr. A. Ingram showed by his investigations of the bionomics of the parasites of wild rodents in Africa in 1928 that infected fleas can live without any host for periods up to three or four months and still retain the power of infecting fresh hosts. It is thus that he explains the persistence of infection on the veldt.]

3. Man is usually infected by way of the skin.

4. *X. cheopis*, when deprived of its normal host, will attack man and animals other than the rat.

5. Epidemics are due very largely to the agency of the rat.

6. The severity of an epizootic depends on the extent of flea prevalence ; a certain degree has to be reached before an epidemic starts.

7. Close contact with diseased animals does not give rise to infection if fleas are excluded.

During the succeeding decade many points were elucidated and amplified by the Plague Investigation Commission under Sir (then Dr.) Charles Martin. Since then, *X. cheopis* has been proved to be the vector *par excellence* ; *X. astia* is less effective because, as Hirst reported in 1927, it lives for a shorter time after infection and is a less vicious biter. Moreover, it has a more restricted distribution, being found mostly along the low-lying coast of Ceylon, the east coast of India and the coast of the Bay of Bengal. Thus, Akyat, on the Burma coast line, has 97 per cent. of *astia* and is free from plague, whereas Rangoon and Moulmein has 50–70 per cent. *astia* and 50–30 per cent. *cheopis*, and are plague-infested. At the same time *X. astia* must not, he says, be regarded as innocuous ; an abnormally high *astia* index appears in some way to be ætiologically connected with an epizootic, a rat-flea index (*astia*) of seven will start an outbreak, whereas a much lower rat-cheopis index will suffice—three or thereabouts. Jorge in 1928 gave the " index of endemicity " as five for the rat-*cheopis* ; that is, when the rat-flea index reached this figure there was grave risk of an epidemic.

In East Africa, Kenya and Uganda, another species of Xeno-psylla, *X. brasiliensis*, was found by Kauntze in 1935 to be a more important vector than *X. cheopis* ; moreover it is the local hut flea.

The human flea—*Pulex irritans*—is infective by laboratory experiment but is not so important in nature because, as compared with that of the rat, the blood of man in plague contains few organisms ; the disease is conveyed from man to man, not by his own but by rodent parasites which attack man if they cannot find sufficient pabulum among their proper hosts.

The cat-flea, *Ctenocephalus felis*, is not only infectible with plague but is an active biter of man. Raybaud found it as active towards man as is *X. cheopis*. This is important in that cats are often kept to kill rats and check their increase, but in view of the fact that cats may develop and transmit plague it is not altogether a beneficial measure.

To return to the years immediately following those of the Indian Plague Commission, we have mentioned above Gordon Tucker's belief that rat to man infection was rare and the opposite more common. He maintained, in 1907, that infected human beings, new arrivals, were the most important source, and next to them infected clothing and merchandise. That fleas in clothing may start an epidemic two recent outbreaks high up in the Andes where there are neither roads nor rats, are witness. It was thought

that drivers picked up infected fleas in their clothing and effects
at a lower level where there was plague and also rats. After
leaving this locality they slept on the floors of inns and guinea-
pigs snuggled up to them for warmth. The first human case of
plague in the Province in three years was a woman whose infection
was preceded by an epizootic among her guineapigs.

We may sum up this part of the subject by saying that it has
been proved that plague is primarily a disease of rodents, and
man becomes a victim of the bubonic form accidentally, as it
were, by interpolation in the rat-flea-rat sequence. It must be
remembered that a parasite which, directly or indirectly, brings
about the death of its host is unwittingly committing suicide.
An infected flea inoculates a rat ; if the infection is sufficiently
severe the rat dies ; this compels the flea to find another host,
and if it does not soon find a suitable rodent and if man is near
it does not hesitate to use him as a *pis aller*. The bite causes
itching and the bacteria regurgitated, or passed in the excreta,
or set free by crushing the insect are inoculated and the man
becomes plague-stricken. Should the ordinary bubonic form
become the pneumonic—again, a more or less fortuitous occurrence
—man can infect his neighbour without intervention of the flea.

As with malaria and yellow fever we thought we knew all that
was necessary about the disease and its prevention when we
discovered their respective vectors and their economics, so with
plague. We are inclined to pride ourselves on the fact that with
the discovery of the mode of infection by the rat-flea we know
all about the epidemiology of plague. We are much mistaken.
There are other factors than the rat, the flea and the bacterium.
Rogers, as we have pointed out, has shown that climate, tempera-
ture and humidity play a part, and apparently no small part, in
plague epidemiology. The genera, species and habits of local
rodents and their ectoparasites, the reasons leading to dissemination
of certain rodents at certain times and so to an apparently sudden
outbreak, the adaptation of one kind of rodent to serve as a trans-
mitter when another is almost exterminated, why one species of
flea should be the optimum transmitter in one district, another
species in another district, why an outbreak should *die away*
except in some spot more or less localized, to constitute an endemic
focus for subsequent extension—all these are still unsolved or but
very partly solved problems.

More is probably involved than we think in the fact that plague
is not essentially a human disease primarily, but one of rodents

to which man accidentally is subject, and, as Professor Greenwood writes : " The vital and medical statistics of the kingdom of rats are still mere fragments " (*Epidemics and Crowd Diseases*, p. 307).

6. SYLVATIC PLAGUE

Sylvatic or silvatic, sometimes ' selvatic,' plague (from the Portuguese ' selva,' wood) strictly means plague occurring as an epizootic in districts not inhabited by man, or plague among rodents in rural (sylvan or wooded) districts where there is no knowledge of the disease. Though of comparatively recent discovery, dating back only three or four years, it can be said to have a history of its own in that in the light of this discovery we find elucidation of obscure matters of more ancient date.

The recognition of the importance of sylvatic plague is due to the work of Chinese investigators in Manchuria, in studying the marmot, tarabagan, *Arctomys bobac*. They demonstrated that rodents suffering from ' chronic ' infection do not aid in propagation of the bacillus ; this depends on animals with acute or subacute generalized infection. What is known as ' chronic plague ' in rodents is of a strictly localized character without bacteræmia, and when plague has become an enzootic the intervals are bridged over by the relatively small number of rodents which suffer from the acute or subacute form. When contracting plague in the autumn the tarabagan may harbour the virus during hibernation —*latent* infection as distinct from *chronic*—and in the ensuing spring the infectivity is renewed and may start an epizootic with bacteræmia. Some of the fleas will carry infection for 200 days and even longer. Sylvatic plague spreads slowly from colony to colony of wild rodents, thus differing from a rat epizootic ; it is said that seventy-two species of rodents are known to suffer from ' spontaneous ' plague. Lesions may be found in lymph nodes without obvious symptoms of infection or gross pathological lesions. Sylvatic plague is dangerous to man only when he enters remote enzootic areas populated by wild rodents.

The subject is one which in the last four or five years has come more prominently into plague history. There is little doubt that it has existed for a long time, some think centuries, in Transbaikalia and Mongolia, and spreading from colony to colony among wild rodents ; to it has been attributed the widespread plague infection of recent years and the epidemic outbreak in Hong Kong in 1894, the sequence being from wild rodent to rat and so to man. In South Africa, California and the Argentine the reverse has occurred of late—sylvatic plague producing, as it were, reservoirs

of the virus.   Wild rodent plague, moreover, tends, it would seem, to produce the pneumonic type in man, as in the Manchurian epidemic of 1910 with its death roll of over 60,000.   Research workers have even concluded that the organism isolated from wild rodents has " a high virulence and a definite pneumotropism." In California the ground squirrel has, between 1903 and 1914, slowly but progressively invaded the coastal areas south of Sacramento River, and the menace to those places where these plague-infested squirrels have been found of late is viewed with considerable apprehension.

A method of discovering the existence of this occult plague in a district was adopted lately (1936) in California, namely collecting batches of fleas from ground squirrels in the field, killing them with chloroform and combing them from the bodies and sending them in buffer salt solution (3 per cent. physiological saline) to the laboratory for animal inoculation.   Though the squirrels themselves showed no signs of plague the fleas gave rise to the disease in septicæmic form in the test-animals.

In 1934 there was an outbreak in Leventué (Loventuel), Argentine Pampas, where a few cases occurred in places far apart during a period of ten weeks.   No rats and no *X. cheopis* were found, but there was an epizootic among *Graomys griseoflavus*, a rodent almost ubiquitous there and of arboreal habits, the prevailing flea (92 per cent.) being *Rhopalopsyllus occidentalis* and the rodent-flea index as high as six.   Mention may be made here that the hare has been found infected in the Argentine (1934) and its danger lies in the fact that it is not a burrowing animal and may travel considerable distances, and man comes into contact with it because it is hunted for food and also for its pelt which is used for making sombreros.   De la Barrera has studied the question in the Argentine Provinces of La Pampa and Rio Negro.   The population is sparse and domestic rats scarce and the paucity of human cases in places widely separated is thought to be due to infected wild rodents—classed together under the local name *cui*, which includes *G. griseoflavus*, one of the Cricetidæ, Cavia, Galea and Microcavia—which come into contact with man by accident only.   They do not penetrate into houses occupied by man unless under stress of hunger ; this happened at the time of the Loventuel outbreak.

There is in America a special ' Sylvatic Plague Committee ' collecting and publishing information.   They find that various of the Sciuridæ—squirrels, marmot, chipmunk, prairie dog—suffer from spontaneous plague, as well as many of the rat and mouse

species. The method mentioned above of inoculation of emulsified pooled fleas was employed for determining infection.

7. LEGISLATIVE MEASURES

Quarantine in this connection will be dealt with in the section on ship-borne plague. Here we will speak of regulations, orders, precautions and such like promulgated by Royal proclamation or by town legislative bodies.

If we regard the sanitary regulations recorded in Leviticus as the outcome of the plague visitation which attacked the Egyptians in the desert, the history of legislative measures dates back to the fifteenth century B.C. For our purposes, however, it will suffice to go back no farther than the fourteenth century A.D. and to mention the legislative measures enacted in Great Britain, for in tropical countries prior to the work of the Indian Plague Commission little was known and less was done, except in those with a littoral where quarantine would be put in force. Legislative enactments are intimately concerned with prophylaxis, building-laws for rat-proofing of houses, etc., which are dealt with in the next section.

It was owing to the threat of plague invading England from the Continent in 1361 that Edward III enjoined the mayor and sheriffs of London to undertake certain precautions, but without much avail, for 200 years later Stow remarks:

It was customary for the people to carry their filth, as entrails of dead beasts and other noisome things, and to throw them into the ditches, waters, fields and highways, whereby the air was in danger of being corrupted ; and so to create infectious diseases in the city (1540).

Part of the oath of office taken by the provost of Dublin in the twelfth year of Richard II's reign was : " Not to suffer any cattle to be slaughtered within your walls, neither to suffer any swine to run about the streets, and to banish all beggars in the time of any sickness or plague." Whether any swine run about the streets of Dublin to-day I cannot say, but the first part of the obligation is certainly not kept. The measures against plague-infected beggars or wanderers were considerably harsher in England and Scotland. When an outbreak was prevailing in London a gibbet was erected at Windsor for effectually disposing of any who came thither from London. In Scotland it was even worse ; three gallows were erected at Aberdeen

that in case ony infectit person arrive or repair by sea or land to this burgh, or in case ony indweller of this burgh receive, house or harbour, or give meat or drink to the infectit person or persons, the man be hangit and the woman drownit.

Leases might be made out reserving part of a house as a plague refuge in time of pestilence. Thus, St. Peter's Abbey at Gloucester has some property at Highnam, two miles from the town, and in a lease dated 1515 is the following :

And upon reasonable summons by the abbat made to the lessee, when the plague shall be at Gloucester or Over, the abbat reserves a convenient part of the mansion house at Hyneham for the residence of himself and his men during the continuance thereof.

Next in chronological sequence came the Sterzing Ordinance of 1534, when Venetia and Lombardy were afflicted and the Tyrol, being a highway between Italy and Germany, was threatened. The regulations included, first, arrangements for solemn procession and prayer ; second, establishment of a friary to which the sick were to be brought, either at night or in the early hours of the morning ; third, a special blood-letter was appointed ; fourth, infected houses were quarantined and contacts isolated for thirty days from the last exposure ; fifth, persons were specially selected to wait upon the sick and others to take food to those in isolation ; sixth, after recovery patients were not allowed to visit the public baths for six weeks ; seventh, innkeepers were prohibited from taking in anyone coming from a house where a death from plague had occurred ; eighth, the dead were to be removed at night in a cart with muffled wheels, so that the people might not be frightened ; lastly, no sick or dead cattle were to be left lying about or unburied in the streets.

A special plague dress for those attending on patients had been used in Italy since the end of the fifteenth century (1493). France adopted it some 230 years afterwards at the time of the Marseilles epidemic in 1720. It has often been depicted and consisted of a long overall, and mantle, breeches, shirt, boots, gloves and hat, preferably made of morocco leather—Ambroise Paré later recommended camlet, serge, satin, taffeta or morocco, not cloth, frieze or fur, which are prone to carry infection. The mask had a beak attached which was filled with aromatics over which the air passed before being inspired, and for each eye there was fitted a disk of crystal.

During Elizabeth's reign several commands and regulations were issued. In 1563 the order was promulgated that the inhabitants from a plague-stricken house were not to go to church for a month—a prohibition regarded much more as a hardship then than now—and a blue cross was placed on every house in which a case occurred. All dogs in the streets were to be killed, a man being paid for this purpose, and all " vagabonds and sturdy

beggars were to be taken up and placed in Bridewell." Within the next week was issued a further order that every man in every street and lane should make a bonfire every Monday, Wednesday and Friday till the plague ceased " if it so pleased God."

In 1570 " Howses having some sicke, though none die, or from whence some sicke have been removed, are infected houses, and such are to be shutt upp for a moneth. The whole familie to tarrie in xxviii daies." People were not allowed to meet in infected houses or to assemble at " funeral dynners." Plays were stopped so that there might be no danger of infection by theatre-crowds and " maisterlesse men, who live idelie in the cyttye, without any lawful calling, frequenting places of common assemblies as gaming howses, cockpitts, bowling allies and such other places, may be banished the cyttye."

On the Continent towards the end of the sixteenth century (1586) measures enforced were more strict. Thus, at Bordeaux, if a case occurred the owner of the house would inform the ward alderman who passed the information on to the Captain of the Plague. The latter then sent a surgeon to examine the patient while he himself, cautious man, waited a hundred paces from the house. If the suspicion was confirmed, the decision as to procedure rested, within limits, with the master of the house. If he decided to remain with the patient and the family the city locksmith was sent for and a special lock was fixed and no one was permitted to leave. The key was given to a neighbour whose duty it was to pass in food to the inmates. When the danger was over, the house was thrown open, cleaned and fumigated, beds and linen washed, after which the family was again allowed to mix with their neighbours. If, however, he decided that the patient could not stay in the house, the latter was at once taken to hospital outside the city walls, the house locked, a wooden cross placed in front of it and the family confined for forty days (quarantine).

As a general measure streets were kept clean of rubbish and the people forbidden to throw filth and garbage in front of their dwellings while the plague continued.

The holding of St. Bartholomew Fair was prohibited in 1593 in London because of the plague.

In 1603, the first year of James I, several proclamations were issued, among them one in July soon after the coronation ordering the nobility of Scotland and all English noblemen and gentry, not being the King's servants in ordinary, to repair homewards to prevent the spreading of the contagion of the plague [a measure

which would be likely to have exactly the opposite effect]. Petitions were received at Kingston and the Knight-marshal had instructions to prevent persons " from infesting the court." St. James's Mayfair and the Stourbridge and Bartholomew Fairs were postponed. In the following year (1604) there was passed *An Act for the Charitable Relief and Ordering of Persons infected with the Plague.*

Forasmuch as the inhabitants of divers cities, boroughs, towns corporate and of other parishes and places being visited with the plague, are found to be unable to relieve the poorer sort of such people so infected, who of Necessity must be by some charitable course provided for lest they should wander abroad and infect others ;

(2) and forasmuch as divers persons infected with that disease, and others inhabiting in houses and places infected, as well poor people and unable to relieve themselves that are carefully provided for, as others which of themselves are of ability, being commanded by the magistrate or officer of or within the place where the infection shall be, to keep their houses, or otherwise to separate themselves from company for the avoiding of further infection, do notwithstanding very dangerously and disorderly misdemean themselves.

The authorities are therefore empowered to tax the inhabitants and property—except the Universities, cathedral churches, and the colleges of Eton and Winchester—for relief of the plague-stricken. It was under the authority of this Act that ' pest-houses ' were provided. Subsequently special collections were made, as in 1645 for Manchester, when the deaths increased to sixfold, and in 1672 for Bridport, Dorset. From these special collections—just as with ' flag-days ' to-day—abuses arose so that in 1670 was enacted " An Act for the discovery of such as have defrauded the Poore of the Citty of London of the Moneys given for their Reliefe at the Times of the late Plague and Fire, and for the recovery of the Arrears thereof."

In 1606 the Order was passed for London " that every infected house should be warded and kept with two sufficient watchmen, suffering no persons to go more out of the said house, nor no searcher to go abroad without a *redd roade* in their hand." Also a marshal and two assistants were appointed to keep out beggars. In the following year plague was increasing in the close environs of the city and the Lord Mayor requested the Lord Chamberlain that all stage plays might be interdicted in Whitechapel, Shoreditch, Clerkenwell, and elsewhere if thought advisable.

At this time the use of coffins was not general and does not seem to have become so for another fifty years *or more*. Thus,

John Davies in *The Triumph of Death*, referring to the plague of 1603, writes :

> Cast out your dead ! the carcase-carrier cries,
> Which he by heapes in groundless graves interres.

Also George Witter, writing on the plague in *Britain's Remembrancer*, 1628 :

> One grave did often many scores enclose
> Of men and women ; and it may be those
> That could not in two parishes agree,
> Now, in one little room, at quiet be.

And Fuller in 1662 :

The long grave stone shown on the south side of the cloisters at Westminster Abbey, said to cover her body [the giantess, Long Megg of Westminster] was placed over a number of monks who died of the plague and were all buried in one grave.

In 1625 Charles I by royal proclamation prohibited the holding of fairs within fifty miles of London, and the Lord Mayor and Court of Aldermen were requested to have infected houses cleaned and especially household material and bedding.

Eleven years later plague was again threatening and the Lord Mayor and Aldermen of London met the justices of Middlesex, Surrey and Westminster to advise them as to measures to be taken. Rates were levied for erection of pest-houses ; churchwardens, overseers and constables were directed to provide themselves with books for instructions and physicians were required to bring up to date a book on remedies against infection and have it printed. Isolation was being evaded and watchmen were set to see that persons did not go in and out or sit at the doors, and more strict enforcement was made of laws against beggars, as many were wandering about, some with plague sores (it was said). In 1639 the rules for removal of the sick to pest-houses and the shutting up of the dwellings from which they had been removed were revived as plague was again increasing. In 1641 further " Orders to be put into execution against the Plague " were promulgated ; among them " That the bill, ' Lord have mercy upon us,' with a large cross, be set upon the door of every house visited by the plague." This custom was maintained, for twenty-four years later Pepys writes (7th June, 1665) :

This day, much against my will, I did in Drury Lane see two or three houses marked with a red cross upon the doors, and ' Lord have mercy upon us ' writ there ; ·which was a sad sight. . . . It put me into an ill conception of myself and my smell, so that I was forced to buy some roll tobacco to smell and to chaw. which took away the apprehension.

8. Ship-borne Plague.   Quarantine and Prophylaxis

In the days of rat-infested wooden vessels the danger of transmission of plague by sea or inland navigation was great ; nowadays the active foci are more in the interior as Tungliao, Shensi and Fukien in China, and in Africa, South America, the Western United States, Madagascar and Java. The ports from which infection is likely to be carried are few ; notably Bombay, Colombo, Rangoon, Moulmein, Dakar, Saigon, Guayaquil and Alexandria. It must be remembered, however, that infected fleas can be transported long distances from the interior in grain and still more in cotton.

Examples of plague, probably ship-borne, at the beginning of the present century are the outbreaks in Hong Kong, South China, and Mauritius, in Cape Colony, Naples and Liverpool in 1901. There was plague also in several Turkish ports, Smyrna, Constantinople and others. The outbreak in Sydney in 1902, studied by Ashburton Thompson, was ascribed to infected ship-rats.

In New Orleans plague did not appear until the facts of transmission were known. It was not until 1912 that the first plague rat was caught there and no human case was seen till two years later. During the ensuing year, 1915, there were coincident outbreaks in man and rodents, and the latter remained infected till 1917. In 1919 there was a second ' human and rodent ' outbreak ; the last human case was seen in 1920 and the last infected rat in this outbreak the following year. Subsequent to this a purely rodent infection was started with arrival of a ship and the development of a human case on board. Dock rats were attacked, but no human case was seen on shore, and the last infected rat was found in January 1925. None has been seen since then.

Dr. Wu Lien Teh in his *Treatise on Pneumonic Plague* writes of the possibility of this form developing on board directly from infected rodents and gives a list of twenty-nine such outbreaks in various parts of the world between 1896 and 1931. One of these is of sufficient interest to warrant a few words. S.S. *Friary*, with a crew of twenty-one, left Alexandria on 22nd December, 1900. During the preceding twelve days the crew had been on shore. The cargo was cotton-seed for Hull, the vessel calling at Algiers on the way. Dead rats were found on board during the voyage. On the day before reaching Hull, on 10th January, 1901, a sailor died, the diagnosis being ' influenza.' Two days after her arrival two more fell sick with pneumonia symptoms, the condition being determined later as plague. By the 21st eight persons

at least had been attacked, including a doctor, who was the only one to recover.

It is of interest to give the dates of the last recorded infections by plague at important ports, on the authority of returns from the *Office International d'Hygiène Publique* :

Europe : Genoa 1909, Havre 1909, Naples 1924 (15th September), Athens 1929 (8th December), Marseilles 1933 (12th August), Azores 1936.

Asia : Aden 1918 (28th May), Madras 1923 (27th January), Calcutta 1928 (11th February), Basra 1930 (25th January), Cheribon (Java) 1931, Semarang, Surabaya (Java) 1932, Beirut 1933 (28th October), Batavia 1934 (27th September), Bombay 1935, Moulmein 1935 (11th May), Rangoon 1935 (28th September), Colombo 1936.

China : Newchang 1907, Swatow and Macao 1912, Amoy 1917, Foochow 1922, Shanghai 1924 (November), Pakhoi and Canton 1925, Hong Kong 1929 (September).

Japan : Formosa 1917 (May), Osaka 1922 (December), Kobe 1924 (October), Yokohama 1926 (July).

Arabia : Jedda 1915 (20th March).

Africa : Lourenco Marques 1908 (September), Djibouti (French Somali-land) 1909, Naona, Mozambique, 1911 (26th May), Zanzibar 1915 (31st March), Capetown 1916 (23rd April), Aura 1925, Lagos 1931 (April), Tamatave 1933 (28th October), Alexandria 1935 (7th May), Dakar 1936 (20th January).

United States : San Francisco 1907 (May), Los Angeles 1924 (November), New Orleans 1925.

Also Havana 1915 (15th August), Hawaii 1935 (18th March).

South America : Guayaquil 1936 (19th February).

Australia : Melbourne 1909, Sydney 1922 (15th July).

QUARANTINE

Quarantine was first known to be enforced in Venice in 1127, when it was enacted that everyone, merchants and others, coming from the Levant had to remain in the house of St. Lazarus—hence lazar house or the lazaretto—for forty days before being admitted to the city. Efforts had been made many years before to prevent plague being introduced across land frontiers, but maritime quarantine was of much later date. Venice was the chief centre of trade with the East and after the Black Death Overseers of Public Health—*proveditori supra la saluti della terra*—were appointed and arrangements made to isolate vessels, persons and goods suspected of carrying infection. Fifty-five years later, in 1403, a maritime quarantine station was established and in 1448 the authorities of Venice drew up Quarantine Regulations on which all the measures since have been based. In 1468 two inhabitants of each *sestiore* were added and in 1485 the Commission was reorganized as a permanent Board of Health. Quar-

antine was fixed at forty days (hence the name) from a mingling of religion and hygiene, this being the period that Christ dwelt apart in the wilderness. Genoa established a lazarette in 1467 and Marseilles in 1476.

Charles II, in council, prescribed in 1664 quarantine for vessels from the Levant, but it was not till 1710 that enactment was passed the result of the menace of plague from the Baltic. This was the first of several such Acts. In 1721 an Act permitted prohibition of commerce for twelve months between Great Britain and any plague-infected country. This was in force for three years, but in 1727 was again passed together with prohibition of entry of persons from an infected place and in 1731 two vessels with cotton goods from Cyprus were ordered to be burned, with their cargoes (C. F. White). In 1752 a Levant Trade Act compelled British vessels, not having clean Bills of Health, to go to one of the lazarettes in the Mediterranean where the cargo was opened and aired, and in 1780 ships bringing grain from the Baltic had to stay in quarantine for forty days while the sacks were opened and the contents exposed to the air. Twenty years later two vessels arrived off the Nore from Morocco with a cargo of hides ; they were ordered to be sunk with the cargoes. Losses were so great and the quarantine dues so heavy that a Select Committee on Foreign Trade called attention to it in 1824 and the following year a Quarantine Act was passed which modified somewhat the previous Acts and was only repealed by the Public Health Act of 1896.

Quarantine, though intended for dealing with plague, applied to cholera also—in fact, in the first half of the nineteenth century more to the latter than to the former and after the 1831 outbreak of cholera quarantine rather fell into discredit and in 1847 England suffered no more severely from cholera than did those countries enforcing quarantine regulations rigorously.

France in 1838 and England five years later had suggested an international conference to consider quarantine problems and in 1851 such a congress met in Paris. Subsequent congresses met in 1866 at Constantinople, in 1874 in Vienna, in 1881 at Washington and in 1885 at Rome. All of these did something to modify the conclusions of the preceding, but all paid more regard to conditions at the port of departure than the health of the ship and its personnel, until the Venice Conference in 1892 at which the first International Sanitary Convention was drawn up, mainly to prevent cholera entering the Mediterranean viâ the Suez Canal.

The two succeeding Conferences, at Dresden in 1893 and in Paris in 1894, dealt also with cholera, the latter in particular with its spread by pilgrimages. That of Venice in 1896 was for the purpose of dealing with plague which had again appeared in Bombay. In 1903 another Conference was held in Paris ; an International Sanitary Convention was formulated to deal with plague as well as cholera ; a permanent International Health Office was proposed and at the Rome Conference of 1907 the *Office International d'Hygiène publique* was instituted with headquarters in Paris. It distributes information on infective diseases, issues reports and discussions on Health matters and has drawn up the International Sanitary Conventions of 1912 and 1926 regarding maritime traffic.

We have mentioned the discredit into which quarantine fell in England from 1831 onwards, and from the middle of the century medical inspection of ships on arrival was substituted, measures being taken according to the conditions found on board. Such Quarantine Medical Officers were part of the Customs Service at first, till in 1873 Port Sanitary Authorities were constituted and the Local Government Board was empowered by the Public Health Act of 1875 to issue regulations for preventing the spread of " cholera and other epidemic diseases " on land or sea, and these powers were extended by the Public Health Acts of 1896 and 1904. In 1907 Cholera, Plague and Yellow Fever Regulations were issued by the Local Government Board and amended from time to time till the International Sanitary Convention was the outcome in 1926, replaced seven years later (1933) by the Port Sanitary Regulations.

The earlier rules had to be on more or less general lines and it was not until the connection of plague with the rat and its fleas was established that scientific protective measures could be formulated.

To complete the picture. The modern methods comprise four main features : 1. Early detection of human or rodent plague in ships or on land. 2. Isolation of persons infected. 3. Prompt destruction of rats and their fleas. 4. Rat-repression or exclusion. We must remember, as Fabian Hirst has shown, that plague may be carried in infected fleas in cargo (as from India to Ceylon) without the disease existing among the rats on a ship.

In accordance with the definitions of the International Sanitary Convention at Paris in 1926 a vessel is regarded as ' infected ' if it has a case of human plague on board, or if the disease broke out more than six days after embarkation, or if plague-infected rats

are found ; as ' suspected ' if a case occurred within the first six days after embarkation, or if there has been an unusual mortality among the rats on board. Though a vessel may have come from an infected port it is regarded as healthy if none of the above reasons is present—no plague, human or rat, on board at departure or during the voyage, and there has not been unusual rat mortality. The measures to be taken before granting pratique are beyond the scope of this work.

Those who do not know the facts are apt to underestimate the fecundity of the brown rat. In Cattegat, where rats were not known, a pair of tame rats escaped from two boys. In less than two years their progeny infested the whole island and exterminated the birds. The figures as calculated reach ' astronomical ' proportions ; thus Rucker states that in five years one pair may have 940,369,969,152 descendants, and in 1872 von Fischer gave the figure in ten years as 48,319,698,843,030,344,720. It is fortunate that the struggle for food and shelter, the existence of disease among them and the presence of natural enemies restrict this exuberant prolificity. Exclusive of damage to structure and cargo on ships the rat was said in 1909 to have caused £15,000,000 worth of damage in England, 200,000,000 francs in France, the same in marks in Germany and dollars in the United States ; in India and China the figure is not known, but it is undoubtedly very high.

In the important ports of Amoy and Canton the rat-infested dwellings in crowded narrow streets with drains in ill-repair have been replaced by macadam roads and reinforced houses ; plague has almost disappeared. In Manchuria, though the roads are wide and drains non-existent plague is endemic because rats find harbourage in walls and roofs of huts.

Retracing our steps we see how the methods of prevention have grown and developed as knowledge increased. Richard Mead in the eighteenth century recommended isolation of the sick, discovery of the source and shutting up of houses. All affected families were to be removed, the sick segregated from the sound who were to be stripped of all clothes, washed and shaved before going to new lodgings. He held it better to remove the healthy to barracks than to transfer the sick. He condemned the procedure of locking up whole families in a house where a case occurred because the result was wholesale infection and high fatality.

Hong Kong is a good example of modification of measures with increase of knowledge. In 1894 infection by the rat was

believed but transmission by its fleas was not known and disinfection of fæces with quicklime or carbolic acid was recommended, because they were believed to infect by respiration, by the alimentary canal or by inoculation (infection of wounds) ; so latrines were held to be a source of plague if they were situated near a dwelling. The patient's clothes were burned, he himself had a hot bath or sponging ; rubbish had to be burned, wards washed down, healthy contacts were removed to an encampment outside and kept under daily observation. Eighteen years later, in 1912, buildings were being erected to exclude rats, dead rats were collected and examined, live rats destroyed, dwellings cleansed with flea-killing mixture ; streets scavenged and refuse removed daily ; house-to-house inspections were made and educative propaganda employed. Similar precautions had been adopted in Japan in 1906. In Shanghai in 1916 an inquiry was held into all unnotified human deaths ; rats were collected for examination, each being labelled to identify the locality where it had been found ; refuse was collected daily and stored in rat-proof receptacles ; drains were covered and kept in repair ; food was protected from rats ; rats were destroyed by poison or trapping, and preventive inoculation was introduced, the Sanitary personnel being the first to submit themselves to it.

Modern views as summed up by the resolutions of the Second Pan-African Conference held at Johannesburg in January 1925, comprised the following :

In towns—concentration on building out the rat and destruction of any found ; in rural districts measures were more difficult and less effective because infection is spread by wild rodents, but much could be done by gassing, poisoning, and trapping. When the rat cannot be kept out, prophylactic inoculation is advisable as the best second line of defence. Officers engaged in the service should wear suitable clothing—boots, leggings, gloves, flea-proof clothing generally and, in pneumonic outbreaks, masks.

As the result of careful fumigation of ships and rat-proofing it is held that " to-day between 80 and 90 per cent. of the vessels that visit United States ports are entirely free from rats and the heavily and persistently infested vessel has become a rarity."

On the principle of casting out devils by Beelzebub the use of the Danysz and the Tiger River viruses must be mentioned. The Danysz virus, now known as *Bacterium enteritidis* var. *danysz*, was isolated from field mice by Danysz in 1900 and introduced for purposes of rodent destruction in 1901. It is not very reliable. Large doses may kill, but small doses seem to confer immunity.

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Discovery of the latter—the Tiger River virus—took place as follows. We must premise by restating that, first, plague must be suspected when rats are found dead or dying in unusual numbers whether they present the signs regarded as macroscopically characteristic, or not, and, second, that rodents are infected with bipolar staining organisms other than those of plague and that such organisms, when isolated, should be checked by experimental inoculation. Thus, in 1926 veldt rodents in De Aar and its environs were dying in numbers and an organism was isolated, not virulent for most rodents but very fatal to gerbilles—one of the chief carriers of plague in South Africa. The same organism was isolated in Cambridge by Murray, Webb and Swann in 1926 and they named it *Bacterium monocytogenes* (now *Listerella*) because a characteristic effect was to increase the large mononuclear leucocytes. It is fatal to gerbilles by ingestion and there was some evidence that the disease would establish itself as an enzootic infection. It was tried over a gerbille belt of country in South Africa some twenty miles long. The disease produced is known as the Tiger River disease of gerbilles and the prepared culture as the Tiger River virus.

After all, when it is possible, as in ships, ports, grain-stores and the like, it is better to build places 'rat-proof' than to try to keep them 'rat-free.' In Java this has been a principle for some twenty years that "if it is necessary to rebuild every village in Java to get rid of the plague, every village must be rebuilt." The Dutch authorities refused as far back as 1920 to accept plague as a necessary evil. In 1910–11 when plague broke out explosively in Java the authorities were unprepared, but the medical service rose to the occasion. House improvement was started at once. In Malang district among a population of 740,000 deaths from plague in the period 1911–15 numbered 22,000. One hundred and forty thousand dwellings were reconstructed or improved and, except single imported cases, there has been no plague there since 1916. Nowhere in the world has house improvement as the chief —almost the sole—antiplague measure been carried out so systematically as in Java. The method is, of course, slow in action, or rather its results are deferred and when an epidemic arises must be supplemented by vaccination. This question is dealt with in the next section.

Intensive work is also carried out in Kenya, Uganda, South Africa and Australia. Where rat-proofing is not feasible, other measures such as trapping, poisoning—by arsenic, phosphorus, barium, squill—or fumigation, as by hydrocyanic acid, Zyklon, discoids, sulphur dioxide and the Clayton apparatus, must be

resorted to. The history of the introduction of these is not particularly of tropical importance and will not be dealt with here, except to mention the method used for testing these at the Haffkine Institute, Bombay. These tests are carried out for determining the minimal quantity of a given preparation required to kill all the rats and fleas exposed to it in an artificial burrow of a given size. It was shown in 1932–5 that a preparation known as 'Calcid,' with only twice the amount of Hydrocyanic acid contained in 'Cyanogas A,' was forty-two times as effective. The experiments carried out at the Institute, under the Directorship of S. S. Sokhey, are practical and of great importance in anti-plague campaigns.

In conclusion: Maritime transmission of plague is dependent almost entirely on the escape of infected rodents from ships and the transfer of their infected fleas to rats on shore. A survey (*Public Health Report, Washington*, 1937, No. 14) of ships at Atlantic ports has found only 8·4 per cent. of the vessels infested with rats, whereas between 1925 and 1927 the percentage was fifty. The factors responsible for this satisfactory state of things are effective fumigation, rat-proofing of vessels, extensive inspection and international certification. Rat-free vessels qualify for reduction of quarantine delays and port dues. To relax the precautions which have brought about these results would be a foolhardy act.

9. Treatment of Human Cases, Remedial and Preventive

Treatment, as regards man, may be divided into three categories: 1. The use of Antiseptics; 2. Serums; 3. Vaccines.

1. The first need not detain us long; it has some historical interest, but as a method of treatment it is no longer employed. Plague being a form of septicæmia intravenous injection of antiseptics is ideal in theory, but has proved on the whole unsatisfactory, if not in vain, in practice.

In the late nineteen-twenties intravenous injection of antiseptics was hopefully advocated, particularly for cases of septicæmic or pneumonic plague. The difficulty, however, is that antiseptics which may be potent *in vitro* do not enhance their reputation when tested on animals *in vivo*. For example, quinone in a strength of 1 in 432,000, mercurochrome in 1 in 76,800, catechin 1 in 48,000, will kill bacteria in fifteen minutes, but on experimental testing *in vivo* they proved disappointing. Others tried in human cases have been iodine, neosalvarsan, electrargol, eusol, gonacrine, methylene blue and formalin. The only one worth

speaking of in any detail is mercurochrome, as reports at first favourable, then conflicting, and finally adverse were promulgated, often as the result of trial in very few cases, perhaps a single case, and the personal equation is not easy to eliminate. In 1928 sixty-four cases of plague were admitted to the Infectious Diseases Hospital, Ikoyi, Nigeria, twenty-five bubonic of whom twenty died, twenty septicæmic all fatal, and nineteen pneumonic, fourteen fatal. To nine of the first (bubonic) 10 c.c. of a 1 per cent. solution of mercurochrome were given intravenously and two recovered ; in nine other cases, in addition to the mercurochrome intravenously, injections of thymol-camphor-iodine were made into each bubo and three of these recovered, and it was noted that the intrabubonic injection was followed by a lowering of temperature within twelve hours by about a degree more than the mercurochrome alone. Opinion on the effects of the treatment would have to be very guarded, based on so small a number of patients ; all we can infer is that with mercurochrome alone seven died out of nine, with mercurochrome and intrabubonic thymol-camphor-iodine six died out of nine, and of the remaining seven all died—slight evidence in favour. On the other hand all the twenty septicæmic patients died in spite of their receiving intravenous mercurochrome ; the gravity of the condition is clear from the fact that most died within twenty-four hours. Of the nineteen pneumonic cases receiving the intravenous mercurochrome five recovered ; they also received creosote and potassium iodide by mouth.

Subsequently this drug was tried again and again, with conflicting reports on the results and the final, generally accepted, conclusions were stated in a paper read at the Seventh Congress of the Far Eastern Association of Tropical Medicine (1927) when J. F. Caius and B. P. B. Naidu reported that antiseptics—though having a strong bactericidal action *in vitro*, were difficult to assess *in vivo*, and that mercurochrome, active *in vitro*, had no influence on plague in rats or rabbits.

2. *Serum.* The employment of serum in plague dates back to the last year of the nineteenth century. Yersin and, later, Roux prepared antisera by injecting horses first with killed cultures and later with living cultures of the organism. These and other sera have no interest now, except historically. They were subjected to thorough test by the English Plague Commission in India and the conclusion reached (1912) was that they were of little use and did not reduce the fatality rate of the disease in India. During the ensuing fifteen to twenty years antiplague

serum continued to be employed in India for treating cases of the bubonic type. The dose given was 30–40 c.c., no matter how serious the condition of the patient. Some encouraging results were recorded. Thus A. S. Dawson (*Ind. Med. Gaz.*, December 1927) stated that of fifty patients in an apparently moribund condition sixteen recovered after receiving the serum. We must bear in mind in interpreting the results of any form of treatment that bubonic plague is more amenable to treatment, or perhaps we should say, has a lower fatality rate, than the septicæmic or pneumonic. The crux of the whole question of interpreting the results of serum treatment lies in the fact that there is no recognized method of standardizing antiplague sera and the conflicting results which have been published are probably due to this unequal potency and until some way is found by which a standardized product can be obtained, treatment by serum will not rest on a scientific basis for interpretation.

The most recent developments of which mention must be made to bring the subject up to date are those of Sokhey and Maurice and of Norman Walker. Sokhey and Maurice working at the Haffkine Institute, Bombay, produced in 1936 a new serum prepared from horses by intravenous inoculation, first of living avirulent plague cultures, and later of virulent cultures and filtrates of broth cultures of the organism grown for four weeks at a temperature of 27° C. It is early yet to draw any conclusions, but after experimental work on mice, they tried the product on human subjects in Hyderabad and have reported three deaths among seventeen so treated, as compared with thirteen among the same number (seventeen) of controls.

Norman Walker used serum from convalescent human patients. Forty c.c. of blood are taken from the patients when their temperature has been normal for ten to fifteen days, and 10–20 c.c. of serum—the larger dose is better, if sufficient serum is obtainable—are injected on three successive days. Of forty-eight unselected, but not moribund, patients so treated eight died, a fatality rate of 16·7 per cent., whereas of forty-eight controls twenty-three, or 47·9 per cent., died. The method of administration is not detailed in the report (*Ind. Med. Gaz.*, August 1937), but arrangements are being made for storing the serum of convalescents for the treatment of cases in an early stage in the next outbreak.

Personal Prophylaxis

The use of antiseptics and of serums has been directed to the actual treatment of patients ; personal prophylaxis since the

beginning of this century has been aimed at by employment of vaccines.

The first of these was *Haffkine's vaccine*, broth cultures killed by heating to 65° C. The dose of this was 3 c.c. and immunity was conferred in about a week and persisted, it was held, for several months. More will be said of this later. Very soon afterwards, in 1900, Lustig and Galeotti produced their ' prophylactic,' which was a solution or emulsion of the nucleoproteid obtained by growing the organism in solid media. They claimed for their preparation that by animal experiment with rats, rabbits, guinea-pigs and monkeys they were able to prove its prophylactic efficacy, and also that its use in man caused no disturbance, local or general. Further, they affirmed that the immunizing properties of entire cultural fluids were due to the nucleoproteid constituent which they had isolated and that it was better to employ the single isolated active substance than the same with the addition of non-immunizing substances, and, as an outcome of this, that their preparation had the advantages over Haffkine's in the facts that in the latter these other, toxic, substances are present, but take no part in producing immunity though they cause the reactionary signs which are harmful; also that by the heat needed for producing Haffkine's prophylactic the active substances are changed and the immunizing properties reduced. Finally, that owing to the admixture with other substances Haffkine's product had no accurate standard dosage. Of transient historical interest in this connection mention may be made of the unfortunate effects of antiplague inoculation in the Punjab in November 1902, when eighteen persons died as a result of the preparation becoming contaminated with *Bacillus tetani*.

Next in chronological order came, in 1906, Klein's " new plague prophylactic." This was a tissue vaccine and had a very brief reign. Organs of guinea-pigs dying in five to nine days of subacute plague were dried at a temperature of 46–47° C. over sulphuric acid. The bubo, the spleen, lungs and liver were used and a guinea-pig of 300–400 grammes weight would yield about $5\frac{1}{2}$ grammes of the dried powder. Experimentally 10–15 mgm. would protect a rat against a lethal dose of the plague organisms; for man 5·7 mgm. was injected emulsified in 0·5 c.c. of sterile water.

The subject of avirulent living organisms is an important one and is dealt with below in more detail. We may here sum up the opinions put forward from time to time relative to the use of killed vaccines.

During the late nineteen-twenties the prominent position which

vaccines had occupied in schemes for controlling the disease during the preceding years was being assailed from many sides. It seemed no easy task to make people understand that bubonic plague is primarily a disease of rodents and that the use of plague vaccine cannot limit its duration or extension, and the value of the vaccine in conferring protection on man was questioned in several quarters. Mitchell and Harvey Pirie in Johannesburg stated (1928) that the results deduced from animal experiments tended to show that the feeling of security engendered by the use of prophylactic vaccine rested on an insecure foundation. After extensive use for many years in Java it was abandoned.

Haffkine's preparation has been employed, at first imported from Bombay, later made locally at the Pasteur Institute, Batavia, and the Director, Dr. L. Otten, concluded that though a vaccine can terminate an epidemic of a disease in which man is the centre of infection,

an epidemic of bubonic plague is entirely different. In this case man does not form part of the cycle of infection which continues unhampered from rat to flea and from flea to rat, indifferent to the fact whether man falls a victim or not. The rat provides for the infective agent the indispensable nutrient medium, and thus, not being affected by a general inoculation of the population, as soon as the immunity temporarily obtained by inoculation has disappeared, man is once more exposed to the danger of infection . . . the effects of Haffkine's vaccine are too small to justify any expectation of its application as a repressive measure.

Nevertheless, Dr. Otten records in a report on the *Control of Endemic Diseases in the Netherlands Indies*, 1929, an interesting epidemiological experiment to test the prophylactic value of plague vaccine. He selected a site not yet infected but which, being near an already infected district, might be expected to be attacked in the near future. He vaccinated half the population in such a manner that there were as nearly as possible equal numbers of vaccinated and unvaccinated in each house. Also, equal numbers of men, women, boys and girls were treated and left untreated. When plague did invade the district the returns showed that the unvaccinated were attacked in a proportion of two to one among the vaccinated. The report does not, unfortunately, mention the fatality rates.

Again, in 1932, de Vogel records a wide testing of the value of Haffkine's broth vaccine in Java : 37,224 persons received the vaccine, and 39,004 did not. The fatality rate in the former was about one-half that in the latter, but here the morbidity rates are not given.

In 1928 also reports came from Kenya to the effect that the value of the vaccine depended largely on the manner of its preparation. Agar cultures prepared at the Nairobi laboratory proved much less satisfactory than that prepared by Haffkine's method, but Schütze found at the Lister Institute that agar-cultures were just as protective to animals as Haffkine's. In Uganda inoculation was practised on a large scale with a vaccine prepared at the Entebbe laboratory. In 1926 an outbreak of plague occurred in the town of Jinja but only forty-seven deaths took place and no cases were observed among the contacts when inoculation and segregation were enforced, whereas thirty-five of thirty-eight uninoculated persons who contracted the disease died. In Uganda in 1927 there were 2171 cases and 1863 deaths (86·5 per cent. fatality). More than 90,000 inoculations were made with the Entebbe vaccine and one medical officer of Lira (Lango district) recorded a 40 per cent. recovery among 232 cases, and he thought that the immunity produced lasted for three to six months.

Work carried out at the Haffkine Institute, Bombay, has been of interest and importance to investigators in the Colonies and elsewhere. It was shown that plague vaccines vary considerably in immunizing power and in toxicity. The complaint, by no means an infrequent one, that a vaccine was not efficacious because it produced only a slight reaction had no foundation in fact ; a vaccine may possess high immunizing power with low toxicity. As the result of many years' investigation at the Institute it has been shown that the maintenance of the virulence of plague cultures is of great importance for a laboratory engaged in the manufacture of vaccine on a large scale. Cultures preserved at 37° and at 25° C. steadily lost virulence. Virulent strains, *i.e.* those potent for immunizing, were obtained as primary cultures from severe septicæmic human cases by plating blood from a vein on agar slopes.

The results of vaccine trials are expressed at the Institute in terms of the minimum mouse-protection dose, which is ." the amount of a given vaccine that will protect more than half the mice immunized with a vaccine against the standard test infective dose," or three animals out of five. By these methods S. S. Sokhey, the Director, has shown that vaccines made from cultures grown at 27° C. are apparently superior in protective power to those incubated at 37° C., that heat-killed vaccine is " one hundred and fifty times as potent as the live avirulent vaccine made from the same strain," and that the supernatant fluid in Haffkine's

vaccine is protective while the sediment is not (*Report of the Haffkine Institute*, Bombay, 1932–5).

This brings us to the subject of the prophylactic value of living avirulent vaccines, a matter intensively studied in the past decade. The idea, however, was of much longer standing. More than thirty years ago, in 1906, P. Strong not only suggested but was actually using living avirulent cultures of *P. pestis* (*Arch. f. Schiffs- u. Tropen-Hygiene*, 1906). A culture which in a dose of two agar slopes was not fatal to a series of guinea-pigs he regarded as sufficiently weak to be used for human inoculation. With such a culture he immunized forty-two persons without mishap; he began with 1/100 loop and increased the amount until he was giving an entire agar culture.

For the next quarter of a century we hear practically nothing of the use of avirulent cultures, until in fact a culture of Dr. Otten's was employed, accidentally discovered. In 1934 Otten vaccinated 37,500, or about half the population, of a district near Bandoeng, Java, where plague was raging. Deaths from bubonic plague, as from the second week after vaccination were twenty-three among the vaccinated (14·5 per cent. of the total deaths) and 132 among the unvaccinated (85·4 per cent. of total deaths). The vaccine was made from living cultures of the avirulent strain Tjiwidej, obtained from a plague rat in 1929. Later, Otten states " 400,000 persons have now been vaccinated with living plague without incident or accident. When plague begins to recur among the vaccinated, this is a sign that revaccination is called for." In his report he states that among 37,435 vaccinated there were thirty-eight deaths or 1·01 per mille; among 44,757 not vaccinated there were 213 deaths, or 4·75 per mille, and judging from the recurrence among vaccinated persons, the immunity seemed to be valid for six to eight months.

What came to be known generally as " Otten's living vaccine " found a wider and wider field of application and from its increased use the results were capable of more accurate evaluation. By 1935 an immunity from its employment of 90 per cent. was claimed, that is, for every hundred deaths among the unvaccinated there should be only ten among the vaccinated. If, however, this type of vaccination is to be carried out on a large scale certain difficulties have to be overcome. In the first place, the vaccine being a live one must be very carefully prepared and cannot be stored for an indefinite period, and arrangements for extensive inoculation must not be such as would disturb too much the life and work of the people. The dose found best was one-fifth of an agar culture

emulsed in 1 c.c. for adults ; half this for children below twelve years of age. Occasionally local abscess occurred, but this was rare, only eighty per million vaccinated. In the regencies of Bandoeng and Soemedang, out of a total population of 1,149,273 as many as 1,049,533, or 91·3 per cent., were inoculated of their own free will. Investigation revealed certain contra-indications ; notably that children under three months of age need not be vaccinated, and, as regards others, those with extensive skin disease, any with fever or seriously ill and debilitated from any cause, or in the last month of pregnancy should not be vaccinated. Pregnancy in earlier periods than this was no contra-indication.

A similar vaccine prepared from living cultures of an organism isolated in 1926 from a case of bubonic plague at Antananarivo, was tried in Madagascar in 1933–4, in a district with a population of 107,000 ; of these 5300 were children under two years of age. Of the rest, 46,879 were vaccinated and 55,121 were not. The morbidity rates are not given, but among the vaccinated there were twenty-two fatal cases (4·7 per mille), among the unvaccinated 100 (16·6 per mille), a little higher relatively than in Java.

The duration of the immunity has not yet been determined ; some maintain that it is effectual for eight or even twelve months, but the majority are of opinion that six months is the limit of safety, when revaccination is advisable, because, of course, the reservoir, the rat, is being dealt with by being ' built out ' by reconstruction of buildings, making them rat-proof—a gradual process.

Further use of the vaccine during the next two years but served to confirm the efficacy and harmlessness of the living vaccine prepared from another avirulent strain, known as the ' E.V.' strain. This same strain was used for injecting horses to obtain an antiserum, the amount injected being increased gradually till two bottles of culture were given intravenously. Titration tests showed the product to be superior to the analogous antiserum prepared at the Institut Pasteur, Paris, or at the Research Institute, Johannesburg. Its use in man has not yet been tried sufficiently for any valid deductions to be drawn. The following figures afford testimony to the benefit accruing from the use of this living E.V. strain as a prophylactic in Madagascar. Prior to 1933–4 the average number of cases over a series of years was 3500 per annum. In November 1935 the E.V. vaccine was introduced and the sequence of cases reported from 1933–7 has been 3493, 3605, 3055, 1376 and 596 respectively, and there seems to be no reason why this should not be still further reduced.

In spite of the beneficial results reported from the employment of these avirulent living organisms they are not universally applicable and are moreover subject to certain drawbacks. Thus, comparison with the heat-killed Haffkine vaccines shows that the former may, and usually do, deteriorate very rapidly and that they could not in consequence be issued from a central laboratory for use in a large country, such as India, whereas heat-killed vaccines stored at 4° C., as is done at the Haffkine Institute, retain their potency practically unchanged for months.

Partly the result of experience, partly from custom, different colonies and countries have adopted different types of plague vaccine. Thus, India uses Haffkine's prophylactic, Indo-China the killed vaccine of the Pasteur Institute, in West Africa a lipo-vaccine and an aqueous vaccine of the Pasteur Institute (P.S.T.) are in favour, in Java Otten's avirulent living vaccine, in Madagascar the E.V. living avirulent strain.

Apart from prophylaxis, vaccines and bacteriophage—pestiphage—have been tried in treatment of patients. This would not be mentioned here except that its omission might lead to the belief that measures which theoretically might be thought to be of value had never been tried. As regards vaccines the disease is too acute for them, even theoretically, to be effectual. Phage has been tried experimentally in animals and also in man by Naidu and Avari in India in 1932 ; the preparation employed was a powerful bacteriophage which lysed a twenty-four-hour growth of *P. pestis* in less than two hours, but it proved quite ineffective in practice. In the previous year Guilliny had tried pestiphage intravenously in an outbreak of pneumonic plague in Madagascar, but not one of the patients so treated seemed to receive any benefit therefrom. In 1933, however, Advier reported treating thirty-five cases of bubonic plague with a phage obtained from a patient in Senegal and twenty of them recovered, and he tested the organism isolated from the blood or gland-juice of the patients and found it in each case lyso-sensitive to the phage used. Robic on the other hand found this phage, favourably reported upon at Dakar, useless in Madagascar in either the pneumonic or the bubonic form, although it was fully active against the laboratory strains.

10. CONCLUDING REMARKS

The application of knowledge regarding the mode of contraction of plague, its vectors, its reservoir hosts, is gradually limiting the extent of prevalence, but the question is not infrequently asked,

" Will plague return ? "   Of the two commonest species of rat, the black and the brown, the former is more ' domesticated,' lives in closer association with man and is consequently the more important from the plague point of view.   It was probably introduced into Europe from India some time in the twelfth century and the great epidemics of the fourteenth and fifteenth centuries were the consequence.   As *norvegicus*, the sewer rat, not being an associate of man, replaced *rattus* in Europe, plague died down. This, however, is not the only point ; they habitually harbour different fleas.   *Xenopsylla cheopis* is the special flea of *rattus*, the rat abounding in warm countries, and it is this species of flea which is prone to attack man and to transmit infection from rodent to man.   The chief flea of *norvegicus* is *Ceratophyllus* (now *Nosopsyllus*) *fasciatus*, which is a very capable transmitter of infection among rats but is not very prone to attack man.   The freedom of Europe from plague is in part at least due to the fact that the chief European rat at the present day is *norvegicus* and the chief flea *N. fasciatus.*

Twenty years ago a steamer arrived in the Seine from India with plague rats harbouring *X. cheopis* on board.   A case or two of human plague occurred at Levallois, but the infection did not spread among human beings.   Among the local rats, however, an epizootic arose and there was great mortality observed among them in 1918–19.   The following year more human cases were observed, but the outbreak was soon controlled.   To keep Europe free from plague, therefore, we must not allow the domestic *rattus* again to become established.

The comparative freedom of some parts of India from infection is ascribed by Fabian Hirst to the fact that this transmitter *par excellence*, *X. cheopis*, had been largely replaced by *X. astia*.   This last is now the predominant species in Ceylon.   In India it is more common in the damp and hot provinces of Madras and Lower Bengal where plague is never serious.   Hirst found also that experimental transmission of infection by this flea was not easy ; it rarely bites man at temperatures above 80° F.

Studies carried out in Shanghai afford evidence in support of Hirst's thesis.   A rat-flea survey extending over four years was made by Dr. C. Y. Wu, the Senior Quarantine Officer, and he found that more than 75 per cent. of the fleas were *Leptopsylla musculi*, although the predominating rat—as high a proportion as 85·5 per cent.—was *R. rattus*.   *C. anisus* came next (17·6 per cent.) and *X. cheopis* was found only in the autumn and then in small proportion, 6 per cent.   Dr. Wu, from a study of past

records—and his official position affords him an exceptional opportunity of access to these—concludes that plague has never gained a firm foothold in Shanghai, nor is it likely to do so unless factors other than the prevalence, and above all the seasonal prevalence, of *X. cheopis* come into play.

This, however, is not all. Sokhey and Chitre have shown recently (1937) that wild rats (*rattus*) in India present a very varied degree of immunity to plague infection. Black rats caught in various towns exhibited a wide range of susceptibility and the rat mortality was roughly inversely proportional to that among men. For example, Nasik City had a plague rate of 363·4 per mille, but none of eighty black rats obtained from there died from experimental injection, whereas Madras City with only 0·3 deaths per mille had a rat death rate of 91·1 per cent. Bombay has not for two years shown a plague-infected rat, though 2000 are caught daily and brought to the laboratory for examination and its rats by the experiment were highly immune, with a 7·9 per cent. susceptibility ; nevertheless the human mortality is high, 199·8 per mille. This insusceptibility among rats is not ascribable to continuance of a benign epizootic nor to hereditary transmission, but rather it would seem that different races of *rattus* exhibit different degrees of susceptibility and that in any particular locality the more susceptible tend to extinction, leaving a higher proportion of naturally resistant animals.

Aubert Roche in his work on plague chose for a motto : " La civilization *seule* a détruit la peste en Europe ; *seule* elle l'anéantira en Orient." So mote it be !

CHAPTER XIII

UNDULANT FEVER

In the introductory sections to this work we stated that military medical officers, profiting by experience acquired in warm climates, have contributed in no small degree to our knowledge of disease in the tropics and subtropics. Undulant fever, in its earlier restricted sphere as Malta or Mediterranean fever, is an instance of a disease whose elucidation is attributable almost solely to officers of the Medical Service of the British Army.

Knowledge of a low type of fever with remissions, occurring along the Mediterranean littoral, has been general for many centuries, since the time of Hippocrates (Topley and Wilson, *Principles of Bacteriology and Immunity*). Evidence of this is found in some of the synonyms of the last and present centuries—Malta fever, Mediterranean fever, Neapolitan fever, the Rock fever of Gibraltar, Cyprus fever, the New fever of Crete, and Danube fever. It was first brought prominently to the notice of the medical profession in and after 1854 when cases of a prolonged fever, differing in many essentials from typhoid fever, were observed among the troops engaged in the Crimean War. Many of the British sick and wounded were sent to Malta to recuperate and among them various febrile conditions were observed—malaria, dysentery, typhoid, typhus, cholera—and in addition an ill-defined unclassed type of fever which Marston (in the Army Medical Report of 1863) called *Mediterranean gastric remittent fever*; he himself was attacked by it. He noted the irregular type of fever, the muscle and joint pains, the gastro-intestinal symptoms and the long duration of illness, thirty to ninety days, and even more. His account was admirable as a clinical record and to it little has been added since and nothing has had to be taken away. He thought, as naturally did others, that infection had been acquired in Russia and brought by the patients to Malta, though he noted that there was a greater prevalence in the summer months, that in spite of the length of illness the prognosis as

regards recovery was good and that it was probably not contagious from sick to healthy.

In 1872 appeared the first account given by an Italian, Giulia, in *Gazetta di Medicina*, Naples, his article being entitled *Febri endemichi di Malta* and in the course of the next twelve to fifteen years several articles appeared from the pens of British and Italian writers; Aitken, Duffey, MacLean, Notter, Wood and Veale among the former, Baccelli, Borelli, Cantani, Tomaselli, Galassi, Frederici and de Renzi among the latter. Surgeon-Major Veale's account was published on cases seen by him at Netley in 1879 and in it he pointed out the distinctions between this fever and malaria. The British described it usually under the name Malta fever, the Italians as Febbre di Napoli (Borelli), Miliary fever of Palermo (Frederici) or typhoid fever.

Boileu in 1863 and Chartres in 1866 wrote on Malta fever, but the earliest French work dealing with it at any length which we have been able to trace is an article by Giuffre appearing in 1893 in Charcot and Bouchard's *Traité de Médecine*. For the next decade French writers contributed nothing of note, but in the earlier years of the present century several publications appeared of which the following are the chief: Brault in 1903, Ch. Nicolle in Tunisia in 1904, Gillot in 1905, Cochez and Lemaire the same year, and Soulie and Gardon. In 1903 Hayal in his *Thèse de Montpellier* published a valuable monograph with the title *Contribution à l'étude de la fièvre dite ondulante*. Between 1906 and 1914 many contributed to the literature on this subject, most of them army medical officers in Marseilles (Conor, Huon, Simond, Aubert, and Blanchard), Malta (Thibault, Brun, Vincent, Cillognon, and Schneider), Corsica (Du Bourguet), Montpellier (Vedel, Papon and Tartavez), Ajaccio (Defressine).

The studies of M. L. Hughes, made public in 1897, led him to conclude that the disease had been endemic in Malta and Gibraltar at least from the beginning of the nineteenth century.

Malta fever caused much absenteeism and sickness in the early years of its recognition, and in 1884, three years after Veale issued his account, David Bruce reported that between 600 and 700 soldiers and sailors were attacked every year and that the average length of stay in hospital was 120 days, so that this fever alone accounted for nearly 80,000 days' illness yearly in Malta. Two years later Bruce discovered the causative organism, isolating it from the spleen in fatal cases and he named it *Micrococcus melitensis*; later it was transferred to a separate genus *Brucella*,

so called in honour of its discoverer. Bruce by inoculating the organism he had isolated conveyed the disease to monkeys and again recovered it from them. F. Smith and D. Semple demonstrated by agglutination tests the existence of infection in soldiers sent home to England, invalided from the Punjab and Hong Kong and some of these had never served in Mediterranean stations. C. Birt and G. Lamb carried out agglutination tests in 1889 with the sera of patients in the Victoria Hospital, Netley, and obtained positive results with dilutions up to 1 in 700 in patients from India. They found that normal sera might agglutinate in low dilutions of 1 in 10 (experiments in America resulted in positives as high as 1 in 40 in normal subjects). Many patients in the Punjab and Bombay were diagnosed as suffering from undulant (Malta) fever because agglutination had been obtained in these low dilutions and we may mention in passing that for the same reason or (should we say ?) owing to the same mistake kala azar was thought at one time to be epidemic Malta fever. Afterwards, as is not unusual, the pendulum swung to the other extreme and doubt was thrown on the presence of ' Malta ' fever in India at all.

To complete this part of the story we may anticipate the chronological sequence of events and say that in 1905 Lamb and Pai in India isolated the organism, as Bruce had done originally, from the spleens of eleven cases. It reacted with a known Malta fever serum in high dilution and also produced the disease when inoculated into monkeys.

Returning to Malta ; measures directed towards prevention of infection by general cleanliness and attention to hygiene were found quite ineffectual ; water-supplies were analysed and investigated, drainage rectified and improved, walls of dwellings and hospitals scraped, and dust and refuse removed, but the disease continued its ravages unabated and nearly every patient admitted to hospital contracted it.

In 1897 B. Bang reported the finding of an organism which was causative in contagious abortion in cattle, but it was not for more than twenty years after that the significance of this as regards undulant fever came to be recognized (see later).

In 1904 a Royal Society Commission was established at the request of the Admiralty and the War Office, with Bruce as president, and Bassett-Smith, Klein, Martin, Horrocks, Shaw, Johnstone and Zammit as members, to investigate the fever which was

causing so much sickness and invaliding in the Malta garrison. Their first object of study was to determine how the causative agent entered and how it left the body, and its action on experimental animals. In the following year the problem was solved, almost, one might say, by accident, when it was found that the goat was highly susceptible. The reverse had been thought to be the case because injection of cultures into these animals gave rise in them to no signs of ill-health and they were, in consequence, regarded as immune or refractory. Then Dr. Zammit, of the Malta Board of Health, examining in 1905 the blood of these animals, found that the serum agglutinated the organism, and he concluded that though it had caused no symptoms the organism must have lived and multiplied in the tissues—a condition now known as *inapparent infection*. The milk also of infected goats was proved to contain agglutinins. In the same year J. C. Kennedy discovered that the organism was excreted in the urine of these animals.

Further examination revealed the astonishing fact that nearly half (41 per cent.) of the 20,000 goats in Malta were infected and that some 10 per cent. were actually excreting the organism in their milk—hence another, later, synonym of the disease was Goat Fever. Monkeys fed with the milk contracted the disease just as they did when inoculated with the organism.

The results of the investigation carried out by the Commission in Malta were summed up by Bruce as follows:

1. Fifteen per cent. of 525 dock hands at Malta gave a positive serum reaction, thus proving the existence of ambulatory cases.

2. Nine out of twenty-two examined were excreting the organism in their urine and probably about 2 per cent. of the native population are thus excreting them and such constitute a possible danger.

3. Mules and dogs in Malta are infected as well as goats. About half the goats are infected and 10 per cent. excrete the organism in their milk.

4. The chief source of infection in man is goats' milk.

In consequence of this Maltese goat milk was struck out of the dietary of the garrison and the disease incidence at once began to fall. Among the general population who continued its use there was no corresponding drop—an excellent and instructive control test to the experiment on the garrison. As the knowledge and the application of it extended to the people the incidence among them fell also, but not to the same degree as they could

not be controlled in the same way as the troops or naval personnel. The following table shows very impressively the results of the application of this preventive measure.

Year.	Cases of Undulant Fever among		
	Navy.	Army.	Civilians.
1905 . . .	270	643	663
1906 . . .	145	163	822
1907 . . .	12	9	714
1908 . . .	6	5	502
1909 . . .	10	1	456
1910 . . .	3	1	318

The fall in incidence must not be ascribed entirely to this happy discovery for, as the Mediterranean Fever Commission Report 1905–07 shows, it had been falling prior to this. It was remarked that in Malta the officers and upper classes of the civilian population suffered more than the non-commissioned officers and men and the lower classes of the people, but the incidence per mille had fallen from 269·5 in 1859 to 91·2 in 1888. The civil population have continued to drink goats' milk even to the present day and until 1937 pasteurization had not been carried out, and even then quite inadequately, and among them the number of cases had not only remained high but of late has increased greatly. In 1926 there were nearly 600 cases; in 1934 some three times that number.

It was fortunate that cutting off goats' milk from the dietary of the naval and military personnel was followed by such a dramatic illustration of the value of this measure, for in the same year (1905) Johnstone carried out an epidemiological investigation and came to the conclusion that neither food nor drink played a part in causation or spread, nor did dust or personal contact; in the following year Davies arrived at the same conclusions as regards food and drink, but was of opinion that some cases could be accounted for by contact, either direct or indirect through the agency of mosquitoes, the latter theory having the support of Zammit.

Further and more intensive investigations were at once taken in hand and medical officers in India found cases to be far from rare in the Punjab, and W. C. H. Forbes found also that goats there were infected. The disease was shown to be widespread in North-west India and especially in places where the British

troops were stationed. C. Birt reported in 1906 that he had found Malta fever endemic in the Orange River Colony and that goats' milk was much used in the district. The presence of the disease in Rhodesia was observed after goats had been introduced and among children drinking unboiled milk the number attacked was four times as great as among those drinking boiled milk. In the *Journal of the Royal Army Medical Corps*, 1906, is an interesting account of an outbreak on a ship, due, it was believed, to the crew drinking the milk of goats brought on board at Malta.

Incidental mention may be made of Ross's view of the causation of the disease at Port Said in 1906. He attributed it to *Acartomyia zammitti*, a Culicide, the larva of which exists only in concentrated sea water. This recalls Zammit's theory of transmission of the infection by mosquitoes.

Evidence that animals other than goats are concerned in the spread of infection was accumulating for some years but the work of the Undulant Fever Centre of the Rockefeller Foundation established in the south of France did much to prove it. This showed, in 1930, that undulant fever was widespread in southeast France ; though cattle are few there sheep and goats are common.

The disease was seen to attack mainly those engaged in rearing sheep and goats and the incidence was highest at the lambing season. Males were attacked twice or even three times as frequently as females. Further, it affected not merely those who drank milk or ate milk products ; in fact, an even more potent cause appeared to be actual contact with the animals or their excreta. The report of the Foundation noted that " cows in close contact with sheep and goats might contract the infection, and excrete the organism in their milk for a long period, and human beings drinking the milk might fall ill with undulant fever." There was no little difficulty in assessing the prevalence accurately because, in the first place, many practitioners were still in ignorance of the disease and diagnosed patients as suffering from enteric fever, tuberculosis, rheumatism and so on. One patient had been recorded and diagnosed successively as malarial, then as suffering from enteric fever, then a streptococcal infection, next influenza, whereas all the time it was a case of undulant fever. Secondly, diagnosis can only be made with certainty by laboratory methods and many practitioners were not within reach of laboratory facilities or they failed to utilize them. Thirdly, in some countries, Great Britain among them, undulant fever

is not a notifiable disease, hence it is advisable to report all cases of prolonged fever of obscure origin or character, in order that bacteriological examination may be undertaken. Lastly, the organism, like *Mycobacterium tuberculosis*, may infect but remain latent and only in a certain (perhaps small) or, more correctly, uncertain proportion are conditions such that symptoms are set up rendering the disease clinically recognizable. It may also be that latent infection may lead to latent immunization—inapparent infection—so that undulant fever is not apparently so common as we would expect among veterinarians.

As the disease came to be studied more and more and investigations into the cause and nature of prolonged and obscure fevers were undertaken, and still more when the fever due to Bang's " *Bacillus abortus* " was shown to be a form of undulant fever (see below) the geographical distribution of the disease was seen to be very widespread. Thus, along the Mediterranean littoral it is present in Italy, Spain, Algiers, Tunis and in Portugal and France ; also in Greece, Turkey, and Palestine ; in Egypt and South Africa. P. D. Strachan in 1906 noted the existence of the disease in the Transvaal, the Orange River Colony and Cape Colony, but stated that up to that time the organism had not been cultivated from the blood or milk of South African goats. In the course of the next ten to fifteen years it had spread widely —at least, if it had existed in other districts previously it had not been recognized—and was reported from Cape Town, East London, Kimberley, Johannesburg, Pretoria and several country districts. It was then thought that infection had been introduced long before by Angora goats and more recently again by importation of Swiss goats. The disease was also present in the Sudan, Uganda, in South-west Africa and in Northern Nigeria. David Bruce, A. E. Hamerton, H. R. Bateman and F. P. Mackie in 1910 discovered its existence, under the local name Muhinyo, in Uganda. They saw fifty patients collected from the eastern shore of Lake Albert Edward and proved it to be undulant fever (then called Malta fever) by culture from the spleen and by agglutination of the serum ; they found also that local goats were infected. Up to the time of this discovery by Bruce and his colleagues the condition had been variously diagnosed as beriberi, dengue and kala azar, although no Leishmania had been seen. Other countries where the infection was known to occur were Arabia, China, the Philippines ; in India the Punjab and North-west Provinces were particularly affected, the United Provinces less, Bombay occasion-

ally, Madras and Bengal rarely except sailors from the Mediterranean. C. N. C. Wimberley drew attention in the *Indian Medical Gazette* of 1907 to the existence of Malta fever in Northern India, in Mian Mir, Rawal Pindi, Murree, Nowshera and Peshawar where goats' milk was commonly drunk by the natives. It was known also in the West Indies and in parts of America, notably Texas, Mexico and Peru and in the Mississippi Valley.

In 1921 Bevan reported that cases were occurring in Southern Rhodesia, though the patients had no communication, direct or indirect with goats (see below).

The connection of undulant fever with the United States is of great importance historically and merits more than the passing mention already accorded to it. The Bureau of Animal Industry, of the United States Department of Agriculture, had observed that the keeping and breeding of goats would be particularly suitable for the peasant classes who had immigrated from Italy, Spain, and Switzerland on several grounds ; the milk was cheaply furnished and compared very favourably with cows' milk, contained a high percentage of fats, was easily digested and by many was preferred to cows' milk for the sick and in the nursery ; lastly, many, perhaps the majority, could afford to keep a goat whereas a cow was beyond their means. Goats, though not in large numbers, had been reared and kept in parts of the United States for some time, particularly in the Southern and South-western States and those where Italian colonists were present in fair numbers.

Members of the Bureau, after visiting several districts in Europe decided on importing the Maltese goat because it was a prolific breeder and a good producer of milk. In Malta they were usually in relatively small herds, from four to thirty-five animals in charge of a single goatherd. They were driven along the streets and customers brought their pails or other receptacles and the animals were milked directly into them at the house-doors.

In 1905 G. F. Thompson, of the Bureau of Animal Industry, went to Malta to collect a herd for the United States. He selected sixty-five and with three goatherds left Malta on the 19th August, 1905. They were quarantined at Antwerp for five days and re-embarked for New York on the 7th September and arrived there on the 23rd of that month and were taken at once to the Bureau's quarantine station at Athenia, New Jersey.

During the voyage all on board drank of the milk and of a crew of twelve whose movements could be traced eight developed " Malta fever." Two others boiled the milk before drinking it, and

two did not like the milk and soon refused to take it. On the second stage of the voyage, after re-embarkation at Antwerp, the complement increased to sixty-four and the goats were giving less milk, so that each person had only a little.

Malta fever was not indigenous in the United States, but while the imported goats were on their way the preliminary findings of the Commission were made public and these tentative findings were brought by the Royal Society to the notice of the United States Secretary of Agriculture.

At the Athenia Quarantine Station there were then remaining forty-four of the imported goats and their sera were tested for indications of infection ; eleven gave good reactions, nine were doubtful and twenty-four negative. On subsequent re-testing some of these last were found to have become positive ; in other words there were signs that the infection was spreading in spite of isolation. Some were found to be excreting the organism in large numbers although the milk was to all appearances normal and by chemical standards good. A few of the animals were off their feed and suffered with diarrhœa, but these symptoms might have been due to one or other of several diseases to which goats are subject, and the majority, even though excreting the organism, seemed to be in good health.

One fact, the importance of which was not known till some years afterwards, was noticed, namely, that the infected goats did not conceive readily ; some of those which did suffered from a septic metritis after parturition and the kids might become attacked with arthritis resulting perhaps in permanent deformity. So severely did the infection spread among the imported goats and their offspring that about a year after their arrival a decision was come to to destroy them all.

We have seen above that cases of disease clinically indistinguishable from Malta fever were from time to time reported where there was no history of the patients having drunk goats' milk or eaten of its products, nor of their having even been in contact with goats.

As already noted, in 1897 Bang in Norway reported the finding of an organism which seemed to be associated ætiologically with contagious abortion in cattle and this he named *Bacillus abortus*.

In 1914 another important and interesting line of investigation was opened up. J. E. Fraum described an organism from the pig which might set up a febrile disease in men who handled the carcases of such pigs. Four years later Alice Evans in America

noted the similarity between the *Bacillus* (or *Micrococcus*) *melitensis* of Bruce and the *B. abortus* of Bang, and both were put into a separate genus, *Brucella*. *Brucella melitensis* it was thought was the form which was infective for man and *Br. abortus* that infective for cattle.

The remark had been made many years before that abortion and, it was thought, a contagious abortion was common among goats of the Mediterranean littoral, and early in the present century bacteriologists at the Royal Veterinary College, London, had proved the existence of *Br. abortus* in goats in England and Northern Ireland. Bevan in 1921 had reported undulant fever in Rhodesia (see above) among persons who had had nothing to do with goats or their milk ; he noticed, however, that abortion was common among cattle there and that the organism responsible for this would set up in man a febrile disease resembling, in fact indistinguishable from, that due to *Br. melitensis*. Further study showed that *abortus* fever was also worldwide in distribution and occurred in the same localities as had been determined for Malta fever, *viz.* Italy, Sicily, Corsica, Spain, Greece, Algeria, Tunis, Palestine, Arabia, India, South Africa, China, South America and the United States.

In 1927 F. E. Robinson demonstrated that the behaviour as regards agglutination and absorption tests of strains of *Br. abortus* isolated from human cases of undulant fever in Rhodesia and strains supplied by F. Huddleson from America was indistinguishable one from the other.

The infection of pigs is far less common than that of man or cattle and, though probably first observed by Keefer in 1922, the causative organism was not determined for a considerable time (Topley and Wilson). It is chiefly restricted to the middle west States of North America and to Brazil and the Argentine, because it is almost confined to slaughterers and packers—in short, an occupational disease in man. Of those engaged in these occupations many harbour the infection in a latent form, as Hardy, Huddleson, Johnson and others have shown. In 1927 J. G. McAlpine and C. A. Stanetz by biochemical methods divided the group Brucella into the *abortus* strain of bovine origin, the *abortus suis* of porcine origin, and *melitensis*, the human strain ; but the issue is not so clear-cut as this. According to some authorities *abortus* infections in the United States are mostly by porcine and not bovine strains, but, according to others, cows may become infected with porcine strains of *Br. abortus*.

Before pasteurization was so widely adopted the presence of

Br. abortus in cows' milk was more common than is generally believed. Thus, according to E. C. Fleischner and K. F. Meyer, in 1917 practically all the certified milk in San Francisco was infected ; E. C. Schroeder and W. E. Cotton in 1921 found 10 per cent. of seventy-seven samples of market milk and six out of thirty-one dairies infected in America ; G. S. Wilson in 1926 from an examination of 488 samples at Manchester showed 5·7 per cent. of single milks and 8·8 per cent. of mixed milks to be positive, and in 1927 C. M. Carpenter and D. W. Baker found nine herds out of fifty infected in Ithaca, New York. More instances might be given, but these must suffice.

Researches carried out by bacteriologists in different countries have proved the natural occurrence of Brucellosis in goats (Bruce *et al.*), cattle (Bang), sheep (Dubois), swine (Fraum, Hayes, *et al.*), mules (Sergent), horses (Dubois), dogs (Kennedy), cats, rabbits, guinea-pigs (Aubert, Thibault), rats and mice. Fowls and ducks may also carry it (Fiorentini, Dubois). Only a few of the chief names have been given, the literature is too large to include all.

When speaking of the history of undulant fever we must not omit the introduction of the Brucellin test for purposes of diagnosis. In 1922 E. Burnet used the filtrate of a twenty-day-old broth culture of *Br. melitensis,* called by him *melitin,* as an intradermal allergic test, analogous to the tuberculin test. The corresponding filtrate of *Br. abortus* was known as *abortin.* The opsonocytiphagic test of Huddleson and his co-workers introduced in 1933 because of the difficulty of correctly interpreting the cutaneous reaction calls for no more than mention here, as evaluation of it has not yet been satisfactorily determined. Its name sufficiently indicates its nature.

Sir Weldon Dalrymple-Champneys, in a special Report on Public Health and Medical Subjects, issued by the Ministry of Health of Great Britain in 1929, sums up the position by stating that in Britain the disease is not very rare. Investigation has resulted in the discovery of unsuspected cases in the United States, in Canada, Denmark, Sweden, Holland, Switzerland and Poland, and it has extended rather rapidly in France and Northern Africa. In France the spread occurs chiefly through goats and sheep, little by the cow ; in the United States by the cow and the pig, the latter particularly in the middle West ; in Denmark and Sweden it is the cow that is the most important agent.

When goats' milk was believed to be the only source there was naturally no reason to expect that there was any considerable

number of cases in Great Britain, but with proof of a bovine origin the matter becomes more grave. Apart from cases in England in which the infection was of foreign acquisition, and laboratory infections which are not altogether rare, Dalrymple-Champneys noted fourteen cases by 1929 and Topley and Wilson record that of 3175 sera examined 101 agglutinated *Br. abortus* at 1 in 40 or higher and estimated that there were eleven cases per million of the population, or 0·001 per cent., while of those exposed more particularly to infection—slaughterers, veterinarians, milk and farm employees—the following were the relative percentages in different countries: *Slaughterers:* in Great Britain 13·1, Hungary 22·6, United States of America 13·7, the Argentine 10·8. *Veterinarians:* in Great Britain 20·6, France 25·0, Denmark 23·4, the Argentine 26·4, the United States 12·9. *Dairy and Farm employees:* in Germany 14·1, Hungary 15·9, New Zealand 16·4, the Argentine 11·8 per cent.

A short recapitulation will indicate how rapidly the disease has spread—allowing, of course, that increased knowledge of the possible presence of the disease and a more intensive search for it tend to exaggerate the significance of the figures themselves. In 1901 only two Departments in France, namely Languedoc and Provence, were known to be infected; by 1926 the disease was present in fifteen and, two years later, in seventeen Departments. In 1910 it was thought to be almost limited to the north coast of the Mediterranean, from Spain to Smyrna, on the east to Beirut and Jerusalem, on the south to Algiers and to Tunisian and Egyptian ports, and to the islands of Sicily, Malta, Cyprus, Corsica, Sardinia and the Balearic Isles. Since then it has been found in—we are loth to say ' has extended to '—Morocco, Tunisia inland, Tripoli, Egypt, Greece, Italy, Southern France, Spain and Portugal. Further, it has been reported from Sweden, Denmark, Holland, Switzerland, Germany, Austria, the Valley of the Danube, the Caucasus, Mauritania, Russia, Poland, the Blue Nile, Aden, Somaliland, the Sudan, Uganda, Rhodesia, South Africa, Northern Nigeria, South-west Africa, India, Ceylon, China, the Philippines, Fiji, the West Indies, Canada, the United States, Peru, Chile, Uruguay, Brazil and Venezuela.

As regards East Africa, Brucellosis has recently been found as the cause of cases of fever hitherto of obscure nature in seven stations in Tanganyika Territory and it is noteworthy that the organism isolated is not purely a *melitensis* or purely *abortus* type, but approaches the Rhodesian type and also *Br. melitensis*.

It used to be said that Mediterranean fever did not pass beyond 46° N. latitude, but this has long ceased to be true, if it ever was ; in fact, there have been large modifications of early views in several points regarding this disease. A few of these may be referred to in conclusion :

Thirty-five years ago Undulant fever was looked upon as a subtropical disease, under the names Malta or Mediterranean fever, whereas it is now known to occur under climatic conditions differing widely between Alaska on the one side and Equatorial Africa on the other. Again, the goat was thought to be the only source by which human beings acquired infection, whereas it is now known that cattle, sheep, horses, dogs and pigs may harbour the organism and transmit the disease. The question of whether fowls and rats are to be included is at present undecided. The term Brucellosis is much more comprehensive than the original Malta fever ; it covers a group including undulant fever with its range of clinical features and also contagious abortion, and infection may be contracted not merely, as was originally believed, by drinking the milk of infected animals or eating milk products, such as cream and cheese, but also by contact such as attending aborting cattle. The problem of prophylaxis is not yet solved, though pasteurization will, of course, destroy the organism.

CHAPTER XIV

RELAPSING FEVER

From the sixteenth to the middle of the nineteenth century when, in 1851, Griesinger gave his detailed account of cases in Egypt relapsing fever was commonly confused with typhoid, typhus and the bilious remittent form of malaria fever. One of the synonyms of the disease was bilious typhoid and, reading descriptions of some of these earlier cases in the light of present knowledge, we can have little hesitation in saying that some at least of the patients suffering from " bilious, mucous, and putrid fevers " with relapse were really victims of typhoid fever. The name 'relapsing fever' was first given to an epidemic which occurred in Edinburgh, 1843-8, and was described by Craigie and Henderson. A hundred years ago and less relapsing fever and typhus often coincided both in time and place—a likely contingency when the vector of each is the same—and the former was often conspicuously associated with outbreaks of the latter. The two might occur together, either sporadically or in epidemics, as in Ireland in 1800 and in 1817 ; at Edinburgh, Leith and Glasgow in 1847, at Cracow the same year, at Peking in 1865, and in the Baltic Provinces in 1865-9. Or, there might be a few cases of the former, relapsing fever, observed during a typhus outbreak as among the troops in the Crimean War in 1854, and in Silesia in 1847 and again twenty years later. Thirdly, an outbreak of relapsing fever might precede one of typhus—commonly seen, says Hirsch—as at St. Petersburg in 1865, in parts of England and at Monmouth in 1868, and at Berlin in 1871. Fourthly, the reverse of this sometimes occurred, an outbreak of typhus preceding one of relapsing fever, as in Berlin in 1868, in England at Liverpool and in Scotland in Glasgow in 1870, and in Posen in 1872.

Infection was known to be conveyed by transport of the sick to fresh localities and was thought to reside particularly in the clothing of the patients. In the Réunion outbreak of 1867 a British vessel brought coolies who had been infected in Bombay

and the disease spread ; for this reason it was known locally as ' coolie fever.' Extension from patients to attendants was particularly noticed and acquisition of infection from clothing was recognized for twenty-five years or more before the causative organism was discovered by Obermeier. In the Edinburgh outbreak, to which reference has been made and when the name ' relapsing fever ' was bestowed, remark was made on the number of laundry-women attacked after washing the clothes of patients. The same was noticed also in the Breslau epidemic of 1868 and Parry called attention to infection from articles of clothing worn by patients during their illness in the Philadelphia epidemic of 1869.

Relapsing fever finds a place in a work dealing with the history and evolution of disease in the tropics and subtropics because it is of great importance in India, Africa, China and other countries with warm climates, but it still prevails in non-tropical countries and has done more widely than at present. In the eighteenth and nineteenth centuries it was common in Great Britain and in various European countries. Before we pass to a more detailed consideration of the former a few words on the latter will not be amiss. Owing to its being spread by lice—of which more will be said later—it is rare now in civilized lands, though it was once prevalent in Europe and large outbreaks occurred in Eastern Europe after the Great War.

The first outbreak on European soil about which we have reliable information is that in Dublin in 1739 ; others occurred there subsequently in 1748 and 1784. In Scotland in 1741 there was an outbreak and thereafter epidemics were recorded in Ireland and Scotland in 1799, 1817–19, and 1826. It was reported from several parts of Ireland in 1842 and extensively in Scotland from 1842–4. This last outbreak is of importance because by it the main characters of the disease were brought to the notice of the medical world. In 1847–8 England was attacked and outbreaks occurred in London, Liverpool and Manchester. Again in 1868 London suffered and the infection persisted in the quarters inhabited by the poorer Irish and the Polish Jews till 1873.

The earliest authentic records of the disease in Russia date from 1833 when it was rife in Odessa, and eight years later in Moscow, but it was not widespread in that country till more than twenty years later, in 1863. In Germany the first reports were in 1847 ; again in this country twenty years elapsed before it became widespread, in 1868, being, it is believed, imported from Russia

and Poland. Subsequent outbreaks took place in 1871 and 1878. Scandinavia's earliest record is of an outbreak in Norway in 1851.

Earlier accounts come from the Levant and the Mediterranean. Röser in 1837 noted it and, from its resemblance to typhus associated with jaundice, described it under the name 'yellow fever.' Aubert in 1840 described it as Smyrna fever, Enzel in 1847 as Bukowina or Levant fever; it was also named Cyprus fever from an outbreak there in 1878.

In Africa the disease occurs in Egypt where, according to F. M. Sandwith, it was first discovered by Griesinger in 1851, and then appears to have been forgotten till 1884, after which sporadic cases and small outbreaks occurred each year. As recently as 1927 Riding and Macdowell recorded an outbreak in Western Dafur Province of Anglo-Egyptian Sudan, which was estimated to have carried off 10,000 out of a population of 40,000. It was believed to have been introduced from the north-west, there having been an extensive epidemic in West Africa and the area bordering on the Lake Chad region of French Equatorial Africa. The case fatality is said to have been nearly 75 per cent. Relapsing fever, therefore, occurs in Central Africa, the Congo, in Senegal, and also in Uganda, Abyssinia and Madagascar. Algiers on the north African coast is another endemic centre.

A deadly epidemic swept across Equatorial Africa from Upper Guinea in 1921. It was thought that infection had been introduced from the Mediterranean for the first cases occurred at Kouroussa among soldiers from Morocco and Algiers. It spread down the Niger and in 1922 invaded the Dori region. During these two years deaths in the French Sudan and the Niger were estimated to have been between 80,000 and 100,000. In 1924 extension took place to the Upper Volta and Koutiala (Upper Senegal), killing at least 20,000. The next year it spread to the Lake Chad region, northern Nigeria and the Cameroons. By September 1926 Dafur was attacked and in one district alone 10,000 died among a population of 45,000, as reported by Atkey, 1929. Altogether it was estimated that 10 per cent. of the people died, the mortality varying between 5 and 25 per cent. The epidemic was dying down in 1928 after which merely small isolated outbreaks were reported.

Other outbreaks of recent years call for mention. In 1924 one occurred in the Gold Coast where *O. moubata* is not known and Dr. A. Ingram, Director of the Medical Research Institute at Accra at that time, proved by experiments on himself and on volunteers that the virus was carried by lice. In Nigeria in 1926

there were 814 cases, 107 of them fatal, among Africans, and in Uganda the same year more than 1500 cases were notified.

The West African variety of relapsing fever appears to be more closely related to the European type than to the *duttoni* group (except the Dakar strain). Epidemics of the louse-borne type have been recorded by Nogue in French West Africa in 1925, by McCulloch and Caffrey in 1925 and 1926 in the Gold Coast and Nigeria (v.s.).

Norman Chevers from a study of Indian records thinks that the disease has existed in that country since the middle of the eighteenth century and that the fever in the United Provinces in 1816 and that of 1836 following drought and famine were relapsing fever. However that may be, the first Indian outbreak to be definitely recognized as relapsing fever was that in the Usufzai Valley near Peshawar in 1852, recorded by Lyall. The fatality rate was 30 per cent. After 1856 epidemics were reported from different parts of the country, Bengal, the North-west Provinces, the Punjab. The Patna epidemic of 1856–7 was described by Sutherland in 1859. In the same year there occurred in Sangur " a disease then unknown to the resident physicians "; it spread towards the Ganges, then between the Ganges and the Jumna and over Bahar and Benares. Since then epidemics have occurred over extensive areas, except in the plains of Bengal, Assam and Orissa. Parts of India, the Himalayas for example, have become endemic foci. In the eighteen-sixties several outbreaks occurred in gaols of the United Provinces and the Punjab, demonstrated by O. Boyes Smith as identical with relapsing fever as it was seen in Great Britain. In 1868 a fresh outbreak occurred, the infection being imported by mule-drivers from Abyssinia. In the Punjab outbreaks have occurred in 1869, 1878, 1891, 1906 and 1920; in the United Provinces it became seriously epidemic in 1917 and by 1920 had spread widely, subsiding in 1924 and almost disappearing by 1929, though still persisting in a few scattered foci. The 1899 outbreak in the Kumaon Hills, which was at the time thought to be a mild form of *mahamari* or plague, was shown by Rogers to be relapsing fever. G. V. Browse in 1913 reported what he believed to be a special form of relapsing fever observed by him at Quetta, on the North-west frontier. Clinically, the onset was sudden, the course mild and the paroxysms short, two or three days at first, later only a few hours.

In China the disease was first mentioned in 1864 when an outbreak occurred at Peking, coincidentally with typhus; in the following year it was reported in a prison at Hong Kong.

The first account of the disease in the United States of America is that of the Philadelphia outbreak in 1844 among emigrants from Liverpool; in 1847 it was reported in New York, and in 1869 again in Philadelphia and again starting among immigrants but spreading from them. In 1871 New York suffered another outbreak, the first cases occurring among Irish immigrants.

In the early days of its recognition relapsing fever was ascribed vaguely to climate, weather, season, soil and such-like, but a study of the known outbreaks till 1880 showed that these had no influence, no direct influence at least. Thus, of twenty-four outbreaks in Europe—Russia, Germany and Great Britain—twelve occurred in summer and twelve in winter ; in India six were studied and of these three—Sangur (1859), Bangalore (1865), Bombay (1877) —occurred in the hot season, and three—Patna (1856), Gazipur (1860), Kasalong (1871)—in the cool season. Race and nationality were thought to play some part because in outbreaks in Egypt, India and Hong Kong European residents were more or less exempt, doubtless from more favourable conditions of living.

Overcrowding played a part in spreading the infection once started because of close contact and passage of vermin ; privation was thought also to be causative and the name ' famine fever ' and ' typhus famelicus ' or ' starvation typhus ' evidence this idea. Murchison regarded relapsing fever, which he called ' recurrent typhus ' as a common result of poverty, want and destitution. In some Indian outbreaks, those of 1865 and 1877 for example, they did coincide with times of famine, but many others showed no such connection. Housing defects, slums and dirty environment, with overcrowding and bad hygiene, have an undoubted share and relapsing fever is almost entirely a disease of the proletariat, a morbus pauperum, as Engel calls it—another analogy with typhus. " The untaxed pay their tax in disease." This has been noted often in temperate climates, but examples are seen also in warmer countries. Thus, in India it has frequently started in a crowded prison and spread thence to the population outside ; the same took place in Hong Kong in 1865. In Réunion it was only the negroes, the coolies and natives living in crowded and filthy huts who suffered ; the whites, better housed and living in greater comfort, were free.

The clearing of all this doubt and surmise dates from Obermeier's discovery of the Spirochæte in the blood of relapsing-fever patients in Berlin in 1868, though the actual proof of its being the

cause was of slower development. Obermeier did not publish his description of it till 1873. The discovery did, however, establish the identity of relapsing fever and what had for long been known as ' bilious typhoid ' and placed on a much more secure foundation the theory of the parasitic nature of infective diseases. Names worthy of note as confirming Obermeier's discovery, with the years in which they recorded their findings are : Engel (1870), Weigert (1873), Birch-Hirschfeld (1874), Heidenreich (1876), Moschut-kowsky (1876), Carter (1877), Albrech (1878) and Koch (1879). Of these Moschutkowsky calls for special mention as being the first to attempt to produce the disease in healthy subjects by inoculating them with the blood of relapsing-fever patients. By so doing he proved not only the communicability of the infection but the specific pathogenic significance of the spirochæte. This he did in 1876–8. He also tried—as did Carter later with the India strain—to convey the disease to laboratory animals—dogs and rabbits—but without success. Carter, however, and Koch later did succeed with apes. Moschutkowsky also proved the identity of ' bilious typhoid ' and relapsing fever by inoculating a man with blood from a bilious typhoid patient containing the spirochæte and producing relapsing fever.

After Obermeier had published his description Lebert in 1874 named the organism *Protomycetum recurrentis* ; the following year Cohn gave it the designation *Spirillum obermeieri*. Later, when it had to be classed among the Spirochætes, some authors, to do honour to its discoverer, called it *Spirochæta obermeieri*, but in accordance with laws of nomenclature Lebert forestalled Cohn and consequently Lebert's specific name must stand and the correct name is *Spirochæta recurrentis* 1875.

Vandyke Carter in 1877 described the strain present in Indian patients in Bombay and was able to convey the disease to healthy persons and to monkeys by injection of patients' blood, and in 1907 Mackie named this strain *Spirochæta carteri* ; it has since been studied by Steen and Townsend (1913), Smith and Graham (1913), Gill (1922), Cragg (1922), Russell, Ayyar and Ubhaya (1924) and Cunningham (1925).

In China the disease was first noted by Hill in Pakhoi in 1904; since then it has been observed in most provinces. Séguin found it in Tonking relapsing fever in Indo-China in 1907 and four years later Mathis and Leger showed that monkeys and white mice could be infected directly from human cases and further that the spirochæte acquired increased virulence by passage through mice.

There are several African strains. The Northern Africa type

has been studied by C. Nicolle and his fellow-workers in Tunis and by the Sergent brothers in Algeria. The Algerian form is known as *Sp. berbera* and the Sudanese as *Sp. ægyptica*. The Moroccan form, *Sp. hispanica* var. *marocana* is apparently identical with the Spanish and was first recorded by Breeze in 1909.

The tropical African disease, African Tick fever, was first described as a spirochætal infection by Cook in 1904. Independently Dutton and Todd in 1905 found the organism in the blood of patients in the Congo and it has been called *Sp. duttoni*. J. Everett Dutton himself died of relapsing fever. In 1906 Breinl and Kinghorn succeeded in inoculating this African *Sp. duttoni* from monkeys into other laboratory animals by intraperitoneal injection—rats, mice, guinea-pigs, rabbits and dogs. In rats the incubation period at first was 12–16 hours and death occurred within a week. If rat to rat inoculation was carried out the incubation period was shortened to 2–6 hours and the disease might run a course as long as forty-five days, during which relapses occurred.

The South American form has caused epidemics in Cuba, in Mexico, in the Panama region, in Colombia, Venezuela, Peru, Uruguay and the Argentine. The organism in Venezuela and Colombia goes by the name *Sp. venezuelensis*, Brumpt, 1921 ; in Panama as *Sp. neotropicalis*, St. John and Bates, 1922. Immunologically it shows differences from European and African strains.

The North American type does not much concern us. It is not very common, but resembles the European variety. The causative organism, *Sp. novyi*, Schellack, 1907, after passage through monkeys is transmissible to rats and mice. This spirochæte was discovered by F. G. Novy (with Knapp) in 1906.

In Persia relapsing fever had been suspected for years but the first real evidence was obtained by Dschunkowsky in 1913. In Asia Minor it occurs from Palestine and from Syria to Iraq.

In Australasia there is no known relapsing fever ; there was one case reported by Morin and Genevray in New Caledonia in 1926, but was thought to have been introduced and not to be indigenous.

Though locally found spirochætes have been given special names—*Sp. duttoni*, *Sp. persica*, *Sp. berbera*, *Sp. carteri*, *Sp. novyi*, *Sp. hispanica*, *Sp. ægyptica*, *Sp. venezuelensis*, and so on—it is probable they are merely physiological or serological varieties of *Sp. recurrentis* They are usually fairly numerous in the first attack, and thereafter become progressively less till a thick film is needed to discover them. Infection can be transmitted by the blood even in apyrexial periods when no spirochætes can be seer

under the microscope ; either they are exceedingly scanty or, it has been supposed, the organism is present in another, perhaps a granular or ultra-microscopic form. In this connection Sir William Leishman's Dobell Lecture (1921) dealing with the life-history of *Sp. duttoni* is of interest. He showed that when the infected insect transmitter, a tick, is kept at a temperature about that of the human body the spirochætes disappear as such but clumps of granules are seen ; these increase in number, become spherical or coccoid, and later there suddenly appear in the tissues small, thin, faintly staining spirochætes, quite unlike the original forms. By dark-ground illumination these small spirochætes could be seen emerging from the clumps of granules which themselves exhibited active motility.

This must be compared with the work of Nicolle in Tunis and Sergent and Foley in Algiers, with the European type, *Sp. recurrentis.* They found in the infected transmitter, the louse, that the original spirochætes disappeared in a few days, but that though no trace of these organisms could be found the insects themselves were highly infective, and later, just as occurred with *Sp. duttoni* studied by Leishman, small spirochætes made their appearance. It is a natural inference that the granules may be a stage of the spirochætal life-history and equally as infective as the spirochæte itself.

Noguchi in 1912 succeeded in cultivating the spirochæte, the principles being a limited supply of oxygen, fresh serum, fresh tissue (rabbit kidney) and a carefully adjusted pH reaction.

Mackie in 1908 gave some details of points of difference between *Sp. recurrentis, duttoni, novyi* and *carteri,* and they affect animals in different ways, some being more susceptible to one strain, others to another strain ; clinically, too, the course of the disease in man differs, in the period of fever, the length of the apyrexial period and the number of relapses under natural conditions ; the serum reactions and interactions differ and, finally, as we shall see below the natural transmitting insects are different.

This section of the subject cannot be closed without reference to an important phase in the history of this disease dating back four or five years only, *viz.* the discovery that the spirochætes present in successive attacks differ from those of the preceding by serological tests. Dr. Helen Russell working in the Gold Coast in 1933 showed experimentally that the first relapse strain B was serologically distinct from the primary attack strain A and if an animal infected with strain B relapsed this second relapse yielded

spirochætes serologically of strain A, and so on alternately. Cunningham, Theodore and Fraser in 1934, when studying infections of Indian relapsing fever, found evidence of two alternating types. But matters became even more complicated when Dr. Russell found that a third type, strain, or variety, might appear in·a later relapse, differing from both A and B. We must not forget that, inoculating spirochætes of the relapse type, we inoculate also immune bodies against the primary attack spirochætes and the passive immunity conferred may influence the type in some way. Jakimow, however, in 1929, found the relapse strain to differ from the original in 50 per cent. of the cases tested.

<div align="center">TRANSMISSION</div>

Two genera of insects have been proved to be active transmitters of the infection of relapsing fever, the tick and the louse. In Great Britain in former days and in parts of Europe and India the latter was the chief vector, but the former is the more important in warm climates. As regards the louse, F. P. Mackie in 1907 showed that the body-louse, *Pediculus humanus*, was the important vector in India. In 1912 Sergent, Foley and Nicolle demonstrated that infection was acquired, not by the bite but by inoculation of the crushed body contents. They showed also that the infection was passed to the offspring of infected lice. Later, Nicolle and Anderson succeeded in conveying the spirochæte of tick-borne relapsing fever to animals by the bites of infected lice and they suggest that the spirochætes of louse-borne and of tick-borne relapsing fever may have the same ancestry or even be identical, modification having been brought about by prolonged passage through different vectors. The last great louse-borne epidemic was that which invaded Central Africa so widely in 1921–8, already mentioned (p. 783).

Some time before this Nicolle was of opinion that relapsing fever transmissible by both ticks and lice would be found, because epidemics in Tunis appeared to begin in the southern districts and spread over the country, although conditions in the south were not very suitable for maintenance of infection in interepidemic periods by lice. He postulated the maintenance of infection by ticks and the spread of it by lice.

David Livingstone was the first to report, or suggest, in 1857, that relapsing fever in Africa is transmitted by the bite of a tick. Since ticks are very widely distributed in Africa, more widely in fact than relapsing fever, there is considerable danger of the

disease being spread by the opening up of trade routes. Christy, however, seems to have been the first to describe the disease in any detail in East Africa, in 1903, and the following year Ross and Milne discovered the spirochæte in the blood of patients in Uganda and in 1905 Dutton and Todd showed that the infection was conveyed by the tick, *Ornithodorus moubata*, not by its bite but by the excreta which are usually mixed with coxal fluid passed out before the insect leaves the host. *O. savignyi*, another species, found in East Africa, Somaliland, Abyssinia, Nubia, Egypt and Southern Asia, does not transmit by its bite but by inoculation of the body contents when crushed. In Eritrea, according to Giordano Mario (1936) relapsing fever is both tick- and louse-borne. Ticks were plentiful—twenty-two species were found—among them *O. moubata*. He found lice on some of the relapsing-fever patients, and therefore surmised that they were also vectors, but did not proceed to prove it.

The agent of transmission of relapsing fever in Senegal was for some time puzzling, for, though the strain of spirochæte was *Sp. duttoni* var. *crociduræ*, search for Ornithodorus was unsuccessful. In 1932, however, Durieux discovered *O. erraticus* in that region. St. Louis was found to be an endemic centre in Senegal. [We may mention incidentally here that from the same tick in Southern Tunis Anderson and Wassilieff obtained a new strain of relapsing fever, the ticks being found in the burrows of a gerbille, *Meriones shawi*, in which the disease exists as an ' inapparent ' infection.] The subject was made even more complex by the finding of Dubois that two strains, from different parts of the Congo, were immunologically distinct.

The life-history of the spirochætes in the tick is of interest. After ingestion they pass through the wall of the alimentary canal to the cœlomic fluid and then penetrate the tissues. The motile spirochæte then disappears (cf. the history in man, v.s. p. 788) and short forms appear after an interval, growing into typical spirochætes, which in turn disappear, new crops arising every six to seven days. There may be a regular relapse in the tick as in man (Hindle).

In the Quetta outbreak of 1913 (p. 784) the tick present was *O. tholozani* (*papillipes*), but whether it was the actual vector was not proved ; bugs and lice were also present.

The Spanish form of relapsing fever is transmitted by other species of Ornithodorus, *O. marocanus* and *O. erraticus*, as shown by de Buen in 1926, which are found capable of infecting monkeys and guinea-pigs by the bite. If lice were allowed to feed on a

monkey so infected these louse bodies, when crushed, infected other monkeys, though by their bite they did not convey infection. The Spanish form is, therefore, transmissible by both insects, experimentally, but Sadi de Buen, who has studied the question, could find no evidence of the disease being louse-borne in nature in Spain. He was able to confirm the development of the organism in lice, noting its disappearance from the insect's intestine. They did not reappear although the louse was most infective on the eighth and ninth days after feeding. [We saw above that the naturally louse-borne spirochæte reappears on the sixth to eighth day.] Failure to reappear is attributed to maladaptation in the louse of a spirochæte habitually tick-transmitted.

In 1921 Brumpt showed that the Venezuelan Panamanian form, *Sp. venezuelensis* (*neotropicalis*) was transmitted by *O. venezuelensis* or *O. talajé*, perhaps by both, and in 1926 Latrchew and, the following year, Moskwin showed the Persian and Central Asian relapsing fever to be transmitted by *O. tholozani* (*O. papillipes*) and in 1931 Weller and Graham demonstrated the part played by *O. turicata* in the sporadic relapsing fever of the United States. They traced the origin of cases to a cave in the Colorado River Valley, in Central Texas, where this tick was found in large numbers. Novy's spirochæte, *Sp. novyi*, is, however, conveyed to man by *O. talajé* (this is referred to again later, as its life-history presents some peculiar features).

Palmer and Crawford in 1933 recorded six cases in British Columbia, the probable vector being *Dermacentor andersoni*, the 'wood tick' which is also the transmitter of Rocky Mountain fever ; this was the first record of relapsing fever in Canada and is mentioned here on that account, though outside the scope of our work.

In 1933 Sergent found that a dog tick, *Rhipicephalus sanguineus* (the vector also of Boutonneuse fever, a Mediterranean form of typhus) was in nature infected by the Spanish-African spirochæte and could transmit the disease by its bite.

The possible part played by rodents merits a few words. We have mentioned the gerbille, *Meriones shawi*, above, but as long ago as 1922 S. T. Darling indicated the rôle of the rat in dissemination of the disease in Panama. There the nymphs of *O. talajé* may be found on *Rattus rattus* and all its three stages on man. The rat is susceptible to infection by relapsing fever spirochætes and the nymphs may convey the disease from one rat to another, while the dispersal of the rat into suburban and rural areas in its

struggle for existence with *R. norvegicus* may disseminate the tick, transmitting relapsing fever into fresh areas. In California also many believe that wild rodents act as reservoir hosts, and in French West Africa and Katanga, Southern Belgian Congo, several species of wild rodents were found to harbour the infection.

According to Brumpt, though tick-borne relapsing fever has rodent reservoir hosts, louse-borne relapsing fever has no host but man.

Nicolle and Anderson, as the outcome of researches carried out in Tunis, have advanced the theory that these spirochætes of relapsing fever were originally parasites of small animals—rodents, for example, which are known to be reservoirs—infection being transmitted by their ectoparasites (species of Ornithodorus) living in rodent burrows. These ticks in their adult stages feed on larger animals, and human beings may become infected, at first probably accidentally. When, in time, the virus became adapted for living in man, it acquired the ability to live in human ectoparasites— the louse—and so might be carried by man to attain almost a world-wide distribution. We may see in this, which seems a plausible explanation, an analogy with louse-borne and tick-borne typhus.

That the primary vector was the tick of the Ornithodorus genus is supported by the fact that almost any strain of relapsing-fever spirochæte can be transmitted by various species of Ornithodorus. Thus *O. moubata* and *O. savignyi* can transmit *Sp. duttoni, Sp. hispanica, Sp. marocana, Sp. sogdiana, Sp. normandi*; *O. erraticus* can transmit the second, third and fourth of these. Experimentally, it has been found that transmission is possible through several generations when the tick is a natural carrier, but the sequence soon fails if it is a strange host; for example, *O. moubata* transmits *Sp. duttoni* indefinitely, but *Sp. hispanica* for three generations only.

Apart from lice and ticks the bed bug has been shown by Rosenholz in 1927 to harbour the spirochætes of relapsing fever in its body fluid after they had disappeared from the intestine. Moreover, they retained their virulence and might, therefore, convey infection by inoculation of their fluid when they were crushed. Their bite was not infective.

The subject of the vector is of more than mere historical academic interest. The tick-borne relapsing fever differs from the louse-borne in several points which may be, and probably are, of epidemiological importance. The following are a few of these:

The tick-borne (A) may have certain lower animals, rodents, as reservoirs, the louse-borne (B) has not; A is rather a place or a house disease, infection is found to persist in ticks found in certain houses or camping sites. Ticks remain infective throughout their life (and for two generations) and they can remain alive without food for two years, perhaps longer, they lurk in walls and floors and on the ground, and so do not spread the disease in the way that lice do by human transport as they do not stay on the human body. From the clinical aspect, the spirochætes are usually less numerous in the blood in the tick-borne and the fatality is lower than in the louse-borne, the fever spells are more intense but of shorter duration and complications are more common. Finally, the spirochæte is more readily inoculable into laboratory animals, rabbits, mice, dogs being susceptible to the tick-borne organism, and not only the monkey and the rat as in the case of the louse-borne. The Algerian form, *Sp. berbera*, and the Sudanese, *Sp. ægyptica*, for example, are louse-borne and have little pathogenicity for laboratory animals, whereas Nicolle was able to transmit the infection by *O. marocanus*, a tick infesting the burrows of the porcupine, the fox, badger and small desert rodents, in addition to the usual laboratory animals.

A few words in conclusion and by way of summary. The infection of relapsing fever was primarily one of small mammals transmitted from one to the other by their ectoparasites—probably some species of Ornithodorus, and by the intervention of these ticks the virus was conserved. Human beings becoming, to a great degree accidentally, infected by these ticks, in the adult stage when they preyed on larger mammals, pediculi intervened and the spirochæte became adapted to this insect while retaining also its transmissibility by the tick. This increased adaptability to the louse ensured extension of infection widely in the world.

As regards vectors, or possible vectors, a fact often forgotten must not be lost sight of in infection experiments, namely that in determining whether an insect is a natural vector only natural methods of infection should be taken into account. It does not by any means follow that because fluid from a crushed tick is infective the tick in question is the transmitter of that particular virus.

The work of Mathis at Dakar in 1927 is of interest in this connection. By means of cross-immunity experiments he showed that the infecting organism of shrew mice, *Sp. crociduræ,* was the same as that found in the local cases of human relapsing fever.

These animals were consequently presumed to be the reservoirs of the infection. The method of conveyance, however, was not known. In the burrows of these small mammals nymphs of an unidentified tick were found by Mathis and it is possible that they were the vectors. It is certain that there was an endemic form of relapsing fever at Dakar due to *Sp. crocidurœ.* Nymphs of *O. moubata* fed on infected animals would transmit the disease to the healthy, but adult ticks so fed did not. Possibly nymphs once infected may remain so˙and transmit infection after becoming adult, but apparently the principal vectors were the nymphs and it was believed that transmission by adult ticks and infection of larger mammals, including man, was of more recent development and took no part in maintaining the virus in nature.

The question of immunity˙presents interesting problems yet unsolved. Mention has been made of the new properties acquired after each relapse, the relapse strain showing differences from that of the preceding attack.

More important is the epidemiological fact noted in Nyasaland in 1928 that natives in tick-infested areas seem to possess a distinct tolerance of infection, if not immunity. Blood-smears from these natives may reveal heavy infection though the symptoms produced are slight, whereas natives coming in from other districts might suffer severely though their blood showed few spirochætes. Natives living in tick-infested areas are, moreover, aware that they lose this immunity if they leave the district for a time and, in fact, some are said to take ticks with them when they go away and allow them to feed periodically with a view to maintaining their immunity.

Lastly, relapsing fever has been suggested and tried as a therapeutic measure, like malaria, for syphilis. On account of the mildness of the fever set up *Sp. hispanica* has been considered the safest. Más de Ayala in 1931 recorded 230 cases treated by intravenous inoculation of 2–3 c.c. of blood taken from a relapsing-fever patient during the febrile period. A further advantage from using this strain is that it can be maintained in guinea-pigs. The virus can be transported either as blood defibrinated and sealed in glass pipettes, when the virulence is retained for twenty days at room temperature, or the infected ticks may be allowed to feed on the patient to be subjected to the treatment of pyretotherapy.

CHAPTER XV

MELIOIDOSIS

Melioidosis is in the main, and in the first instance, a disease of rodents, human infection being of the nature of an accidental happening and fortunately of rare occurrence for, as with other infections fundamentally of rodents, when man is attacked he reacts badly and the fatality rate among human beings is very high.

We will first give a brief sketch of the main points in the history of this disease and afterwards deal with some of them in more detail for the information of those who wish to follow its history more minutely.

This disease among animals first came into prominence in 1913 when an epizootic broke out among the guinea-pigs and rabbits at the Institute for Medical Research, Kuala Lumpur, Federated Malay States. It had, however, been described two years before this in Rangoon among vagrants, many of whom were morphine injectors. Whitmore and Krishnaswamy described the condition as seen post mortem among the bodies sent to the mortuary. In 1917 Dr. A. T. Stanton (later Sir Thomas Stanton, Chief Medical Adviser to the Secretary of State for the Colonies), when Director of the Research Institute, saw human cases of this disease in Kuala Lumpur, isolated and identified the organism and succeeded in reproducing the disease in animals, both by feeding and by in-oculation. No cases were seen—at all events none were recognized —outside Burma and Malaya until 1925 when Pons and Advier recorded cases in Indo-China. Two years later a European patient was seen in Ceylon by Denny and Nicholls, and again two years later another European case was recorded by Mesnard, Joyeux and Gaulène in Tonking, Altogether by 1932 when Stanton and Fletcher published their work on the disease eighty-three human cases had been recorded : thirty-eight in Burma in 1911-12, thirty-nine in Malaya between 1917 and 1929, five in French Indo-China (1925-30) and one in Ceylon in 1927. Forty-one were Indians, twenty-three Burmese, twelve Chinese, six Europeans

and one Annamite. A few others, not included in these, were seen by Knapp and Krishnaswamy in Rangoon in 1915 and 1917.

There can be little doubt that the disease is more common than these figures would lead us to infer. The Malayan cases, for example, were in hospitals situated near the Kuala Lumpur laboratory and between 1927 and 1930 fourteen cases were observed among 3068 autopsies, or 4·4 per mille. Since patients came from all parts of the State of Selangor and there were some 45,000 deaths in the State annually, if this proportion holds, those dying from melioidosis would number about 200. Moreover, there is no reason for thinking that the disease is confined to those places where it has up to the present been detected ; diagnosis is not often made during life and even after death only in places where there are facilities for laboratory investigation.

The Malay States, Ceylon and the Netherlands Indies are the only countries where the infection is known to attack animals. In Kuala Lumpur it has been seen in guinea-pigs, rabbits, rats, cats, dog and horse. In Colombo a cow was found to be infected naturally. The mode of infection is not yet settled. Early cases afforded examples of transference by inoculation, in fact in the earliest records it was known as *morphine injectors' septicæmia* and was thought to have been conveyed by the syringe, although the primary lesion could not be detected.

The most probable route of infection, however, is oral, infected food or drink, contamination having occurred by excreta of diseased rodents.

The above is a very general summary of events ; in the sequel the record is given in more detail :

In the *British Medical Journal* of 1912 appeared an article by A. Whitmore on an Infective Disease occurring in Rangoon. He noted that the condition bore a striking resemblance to glanders —a septicæmia with gross lesions in the internal organs, especially the lungs. The organism associated was in size about equal to that of *Pf. mallei*, the causal organism of glanders. It grew luxuriantly on ordinary peptone agar, and on salt agar formed long tangled filamentous masses ; on glycerin agar a wrinkled culture and in broth produced a pellicle. Young cultures consisted of organisms having an active serpentine motility. Professor Eyre found that it further resembled the glanders organism in giving the Straus reaction in guinea-pigs.

In the *Journal of Hygiene* the following year Whitmore gave a fuller account of thirty-eight cases seen by Krishnaswamy and

himself in Rangoon ; many were morphine injectors. In 1914 septicæmia broke out among the laboratory animals at Kuala Lumpur Institute for Medical Research and this was studied by Dr. William Fletcher who showed that infection was conveyed by contaminated food.

Three years later A. T. Stanton, in conjunction with P. H. Hennessy, reported outbreaks of a disease resembling cholera in certain clinical features, but they observed that in some cases death might occur from septicæmia with lesions like those of miliary tuberculosis in lungs and other organs, after the patients had apparently recovered or rallied from the initial attack. An organism which will be described more minutely later was obtained from the lesions post mortem and in subsequent cases during life from the blood, urine, sputum and cutaneous vesicles. They were able to reproduce the disease in animals—guinea-pig, rabbit, rat, white mouse, monkey, sheep and goat—and to find the infecting agent in the excreta of these animals. The same year (1917) Krishnaswamy reported in the *Indian Medical Gazette* that he had seen more than 200 cases in Rangoon. In 1918 Stanton found several cases of natural infection in animals (cats) and suggested that in nature the disease was one of rodents, man being accidentally infected by food contaminated by animal excreta. The following year Fletcher compared the organism isolated from cases in the epizootic he had studied with that of Stanton and demonstrated their identity.

In 1921 these authors had under observation two more human cases ; one was acute and rapidly fatal, presenting extensive abscess formation in the lungs, liver and spleen ; the other was chronic in course with lesions limited to the skin and subcutaneous tissues. Blood was taken from the latter patient and his serum was found to agglutinate the organism in as high a dilution as 1 in 3000. They named the organism *Bacterium whitmori* in honour of its first discoverer and designated the disease Melioidosis from its resemblance to glanders, deriving the term from the Greek μηλίς, a word used by Aristotle for " a distemper of asses " and οἶος = like. As the stem of the first is μηλιδ—the name should by strict etymology be ' melidoidosis,' but euphony omitted the ' d ' ; more correct, perhaps, would have been ' malioidosis,' from μᾶλις, a term in Hippiatrica for " a distemper of horses and asses," probably glanders. This has the stem μαλι—and needs no ' d ' in the compound. The disease had in former years gone by the names of pseudo-enteritis or pseudo-cholera. By 1925 fifty cases in man had been recorded, comprising 38 in Rangoon, 11 in Kuala

Lumpur and one in Singapore. As regards race 25 were Indians, 23 Burmans, one Chinese and one European. All but two had been fatal ; one recovered after a long illness, the other was still alive after an illness of two years ; he still suffered with chronic discharging sinuses.

Laboratory animals were readily infectible by any of several routes : by feeding, by inhalation, inoculation or scarification, or by way of the mucous surfaces—conjunctiva, vagina, etc. Subcutaneous injection was followed by rapidly fatal septicæmia ; scarification by local induration, caseous ulceration, suppurating lymphadenitis and death in three weeks. Feeding or inhalation proved fatal in a fortnight or less, with caseous ulceration of the mucosa and deposits in the internal organs.

Symptoms in human patients were not characteristic ; they might resemble cholera or enteritis or even plague, or, when pustules and abscesses were prominent features, glanders.

Melioidosis has many points in common also with tularæmia ; among them may be mentioned that both are diseases of rodents accidentally attacking man ; they infect in various ways, produce a septicæmic type of fever lasting for two to three weeks, commonly present a suppurative lymphadenitis following a scratch or a prick ; if the infection becomes generalized miliary nodules are found in the viscera, and finally, non-fatal cases recover slowly after a protracted convalescence. This comparison between glanders, melioidosis and tularæmia is referred to again later. We now return to the chronological history.

The next case to be recorded was that seen by Pons and Advier at Saigon in 1926—a woman dying from the disease which she was believed to have contracted from an animal source. A culture of the organism was sent to Kuala Lumpur where it was examined and tested by Stanton and Fletcher and found to be more highly virulent than any of those previously isolated.

In 1927 was recorded, by Stanton, Fletcher and Symonds, the first case in a horse, an animal which till then had seemed to be refractory, differing thus essentially from glanders. The organism was isolated from a purulent nasal discharge and the animal's serum agglutinated the type strain of Pf. whitmori in a dilution of 1 in 8000. The horse had been imported into the Federated Malay States from Australia, and it was kept alive for eighteen months after the organism had been isolated from it ; it did not react to the mallein test. It was clearly much more resistant than the small laboratory animals and this was further confirmed by the fact that when it was destroyed no active lesions were found

internally, nor was the organism isolated from the viscera; in short, it seemed to have recovered, bacteriologically.

In 1929 another European case, the third, was recorded by J. Mesnard, B. Joyeux and Gaulène. Infection in this case was thought to have been contracted by ingestion of food contaminated by the dejecta of rats. The history obtained of this patient was a sudden onset with rigor, high temperature, pain in the back, and mental hebetude; on the fourth day of illness a papular rash was observed on the abdomen, but the general state showed some improvement. Later, the fever returned, pneumonic symptoms supervened and the patient died comatose on the thirteenth day of illness. Examination revealed no malaria parasites, absent Widal reaction with members of the enterica group, but a positive Weil-Felix reaction with the indole-negative type of *Proteus X 19*, negative with the indole-positive strain. No explanation was forthcoming for this; guinea-pig inoculation was negative for typhus and hæmoculture from the patient yielded a growth of *Pf. whitmori.*

The following year, 1930, another European case was reported, this time in Cambodia, the patient being a Russian ordinarily resident in Siam. Hæmoculture yielded a cocco-bacillus and the illness was at first thought to be plague, but the organism was motile and proved to be *Pf. whitmori.* The patient died in a few days. The same year a young European officer, who had been four months in Cochin-China, was seized with chills and fever and twelve days later was admitted to hospital in a torpid ' typhoid ' state, but though typhoid was naturally suspected he was noticed to have also an orchitis and epididymitis. A blood culture was taken and Whitmore's organism was isolated. Death resulted and at the autopsy 100 c.c. of thick pus was evacuated from the tunica vaginalis and from this also the organism was cultivated. The intestine was free from ulcers, typhoid or other.

We see that reports of cases are now becoming more numerous and issue from fresh districts. In 1931 a patient was seen in Singapore; he had been suffering with fever for a week and on the fifth day a rash appeared, a mingling of papules, vesicles and pustules, on the face, neck and trunk, thickest on the cheeks, least on the forehead, few on the chest, many on the abdomen; there was basal consolidation of one lung. The case was diagnosed, as one would expect, as smallpox, but its true nature was determined bacteriologically. The patient died.

The same year P. H. Martin, at the Kuala Lumpur Institute for Medical Research, in the course of examining cerebrospinal

fluids found three with marked eosinophilia and from each of these he succeeded in isolating *Pf. whitmori*, the first time the organism had been obtained from the central nervous system.

We next hear of cases in the Netherlands Indies. The first was a native in West Java, fifty years old in 1931, exhibiting chronic lesions of the skin. In the left thigh was a thickening and there were nodules, practically painless, but with fistulæ discharging greenish-yellow pus. From this the organism was isolated.

Two years later another was reported, by A. A. Hulshoff, as having suffered at the onset with high fever, followed by chronic sepsis and intermittent fever for eighteen months. Pulmonary symptoms were marked and he had subcutaneous abscesses and an abscess of the prostate. Diagnoses made from time to time were : Typhoid fever, glanders, syphilis, tuberculosis, mycosis, sporotrichosis and septicæmia. The organism was isolated and the diagnosis of melioidosis determined. In 1934 Pet and Fossen reported a fatal case in the Netherlands Indies.

Between 1932 and 1934 we find reports coming in of patients in Indo-China. Thus, in 1932, L. Souchard recorded ten cases, varying in clinical type. Two ran a hyperacute course and death took place within a week ; six were subacute : of these two proved fatal within a month, two died later on, one was taken away from the author's care when practically moribund and doubtless died soon after, and one recovered. Two became chronic, one with pyelonephritis and one with multiple chronic abscesses of the bones, but recovered after two and a half and six months' illness respectively. The causative organism was isolated from all ten ; from the blood in eight, from the urine of one and the pus in the other. Two years later, in 1934, a subacute case occurred in a soldier, 25 years of age, the fourth to be recorded in the Tonking area. He suffered from a fluctuating type of fever and died after an illness of three months. Autopsy revealed four to five litres of hæmorrhagic fluid in the peritoneal cavity, diffuse inflammation of the lungs with clusters of nodules, pleural adhesions, a sero-fibrinous pericarditis and abscesses in the liver, spleen and one kidney. From the liver the organism was isolated.

In 1935 three more cases were recorded, one in Celebes and two in Indo-China. The first was a Mandarese woman—the fourth case to be reported in the Dutch East Indies—with an abscess in the right gluteal region from which *Pf. whitmori* was isolated.

The first of the two in Indo-China was a soldier in Tonking who fell victim to a very acute attack. The onset was with fever, headache and general pains followed by signs of bronchopneumonia; the liver a little enlarged but not painful; jaundice came on six days later and death took place twenty-four hours after. Blood culture yielded a growth of the causative organism. At the autopsy abscesses were present in both kidneys and patches in the lungs. The origin of the infection was not traced.

The second was a most unusual case, recorded by Marque and Raynal. A woman, 48 years of age, was taking her daughters who were suffering from typhoid fever, to hospital by motor-car. On the way an accident occurred and the car fell down an embankment into a pond. The party was rescued and the mother was taken to hospital with bruises and signs of water in the lungs; she was expectorating blood and blood-stained froth. This symptom ceased next day, but the patient passed into a state of coma-vigil. After another twenty-four hours her general condition improved; then her temperature again rose and she complained of headache and sleeplessness and the pulse became rapid and delirium set in. Blood culture was taken with a view of her condition also being due to typhoid fever, but a growth of *Pf. whitmori* resulted. Death occurred eight days after her admission into hospital. She was in a normal state of health up to the time of the accident; the most probable source of infection would appear to be the pond water contaminated by rat dejecta.

A brief epitome of the foregoing may be serviceable, the events being given in chronological sequence:

1911   A. Whitmore in Rangoon observed at the mortuary bodies presenting lesions reminiscent of glanders.

1912   Whitmore and Krishnaswamy saw thirty-eight patients with similar lesions; all were males and many were morphine injectors and showed abscesses or sinuses at the sites of the injections. Thinking that the injections were the cause of the lesions they called it a septicæmia of morphinists. From the lesions they isolated an organism, *Bacillus pseudomallei*. Experimental work was carried out with guinea-pigs.

1913   W. Fletcher in Kuala Lumpur investigated an epizootic among laboratory animals at the Institute for Medical Research.

1917   Knapp in Malaya saw human cases (recorded in *Indian Medical Gazette*).

A. T. Stanton and P. H. Hennessy observed patients with choleraic symptoms, the survivors developing sinuses and abscesses.

1918   Stanton observed a case of spontaneous (natural) infection in a cat. He and Fletcher pointed out the resemblances of the new disease to tularæmia.

1924 Stanton and Kanagarayer reported two more cases, in one of which the mallein reaction was positive (*Jl. Hygiene*).

1925 By this time fifty human cases had been reported at Rangoon, Kuala Lumpur and Singapore.

1926 Pons and Advier recorded a case at Saigon, and Vielle, Morin and Massias two European cases in Indo-China.

1927 Stanton, Fletcher and Symonds recorded an instance of infection in a horse—the first record among Equidæ. C. R. Denny and L. Nicholls observed a European case in Ceylon, and R. Pons a case in Cochin-China (reported in *Ann. Inst. Pasteur*).

1928 Verge and Pairemaure showed that complement fixation occurred in glanders using Whitmore antigen.

1929 J. Mesnard, R. Joyeux and Gaulène reported a (fourth) European case at Tonking.

1930 Letonturier, Martin and Souchard recorded another European case, an aviation officer at Saigon, and A. Gambier, a case at Pnôm-Penh (Cambodia), a Russian believed to have been infected at Bangkok. Thereafter reports became more frequent and research work more intense.

Verge and Pairemaure carry out researches with Whitmorin, a preparation analogous to Mallein, and Bozelli succeeded in transmitting the infection to the ass and the horse.

1931 C. C. B. Gilmour recorded a case in Singapore (*Malayan Med. Jl.*). Houssiau compared melioidosis with tularæmia.

1932 De Moor, Soekarnen and Walle record a case in Java (*Meded. Dienst. d. Volksgesondheid in Nederl.-Indië*).

Stanton and Fletcher publish their work in *Studies from the Institute for Medical Research, F.M.S. No. 21*.

Martin, P. H., cultivated *Pf. whitmori* from the cerebrospinal fluid of melioidosis cases.

1933 A. A. Hulshoff reports two cases in the Netherlands Indies and states that Roton reported a European case and Salicelli another (a French officer) both in Saigon; Souchard and Ragiot reported two others, Annamites, also in Saigon. The latter recovered after illnesses of 2½ and 5–6 months.

1934 Another case, a soldier in Tonking, and a fatal case in the Netherlands Indies observed by Pet and Fossen.

1935 A Mandarese woman in Celebes, and another soldier infected in Tonking. Also the woman detailed above whose case was reported by Marque and Raynal.

1936 A case in Tonking reported by F. Toullec and M. Riou (*Bull. Soc. Méd.-Chirurg. Indo-China*).

The increase in number of cases is shown by the fact that between 1912, when the first record was made, and 1926 there had been only fifty cases reported, whereas in the next seven years this figure was nearly doubled. By 1933 ninety-five had been notified, distributed as follows: Burma (1912) thirty-eight, Federated Malay States (1917–29) thirty-nine, Indo-China (1925–30) ten, Ceylon (1927) one, Siam and Netherlands Indies (1930–3)

seven. Of this total forty-three were Hindus, thirty Burmans, twelve Chinese, six Europeans and four Annamites ; with the exception of three women and one infant all were male adults. Since 1933 a few more cases, two of them women, have been noted and have been referred to above.

It will have been seen from the clinical histories detailed that varying types of the disease are met with, namely the hyper-acute in which death occurs within a week with symptoms like those of plague, cholera or pernicious malaria ; secondly, acute, killing within a fortnight with typhoid-like symptoms ; thirdly, subacute, proving fatal usually in three to four weeks, sometimes with intervals of remission, with varying localization—epididy-mitis, bronchopneumonia, pulmonary abscesses, phthisis, myositis, parotiditis, liver abscess, pyonephrosis, etc. ; occasionally one of these subacute cases goes on to recovery. Lastly, some run a chronic course, with osteitis, pustular rash, cutaneous abscesses and resultant scarring. This, the so-called ' surgical ' form, is comparatively rare.

So striking at first view is the resemblance between melioidosis and glanders that Whitmore in his first description of the post-mortem findings in a human case in 1913 entitled his paper *A Glanders-like Disease occurring in Rangoon*, and it was not until he found that the lesions were associated with an organism differing from that of glanders that he had any doubts. Both diseases are characterized by the presence of pyæmic nodules, some sup-purating, others caseating ; they show no histological difference. Central chromotaxis and slight tendency to extension, characters regarded by McFadyean as peculiar to glanders, are presented also in melioidosis.

The causative organism, however, though allied in some of its reactions has several characteristic differences. Stanton and Fletcher, for the purpose of comparing the two organisms, obtained five strains of *Pf. mallei* from Java, Muktessar, and the Lister Institute and they showed that what had hitherto been known as *Bacillus mallei* was not a single organism but a group, the members being distinguishable by serological tests. That of melioidosis isolated by them in Kuala Lumpur proved serologically closely allied to the Muktessar strain, but attempts to infect horses with it were not successful. (We have seen above how; later, Stanton and Fletcher found a horse naturally infected.) The organism of Whitmore is fairly resistant to external influences and it is due to man's comparative insusceptibility that cases of

human infection are not more numerous. Were this not so, there would almost certainly have been a serious epidemic among laboratory workers and attendants who had the care of hundreds of infected animals while the investigation was being carried out.

Character.	Pf. mallei.	Pf. whitmori.
Morphology . .	Rod 1·5–3 μ long	Rod 1–2 μ long
Staining . . .	Gram-negative	Gram-negative
Motility . . .	Non-motile	Motile
Conditions of growth	Aerobic	Aerobic
Broth	No pellicle, no odour	Pellicle forms, falls to the bottom ; aromatic odour.
Agar slope .	Oily, pigmented	Oily, metallic, wrinkled, pigmented
Peptone . .	No indole production	No indole
Gelatin . .	Not liquefied	Early liquefaction
White of egg .	Not digested	Rapidly digested
Milk . . .	Clot in ten days	Clot in four days
Potato . .	Glazed, yellow-brown viscid, later chocolate	Similar, but more creamy-yellow, later chocolate, may become wrinkled
Pathogenicity	Weak for rodents, high for Equidæ and man	Weak for Equidæ, high for man and rodents. By experimental inoculation rodents are seen to be very susceptible by ingestion, by cutaneous inoculation, or viâ the mucosæ—ocular, nasal, buccal, vaginal. The cat can be infected viâ the digestive tract and the disease is usually subacute; in the monkey the course is more chronic. Stanton showed that sheep and goat were infectible, pigs were very refractory and the ass and horse but little susceptible. Birds were also refractory
Cuti-reaction	Positive in glandered horses ; rarely positive to whitmorin in glandered patients	Positive to mallein in melioidosis patients ; horse with melioidosis negative to mallein
Straus's reaction	Positive	Positive
Complement fixation	Positive, with one type (Muktessar) which is closely allied to Pf. whitmori	Positive

Moreover, though the organism can be isolated from sputum, urine, discharge from ulcers and sinuses, patients can, nevertheless, be treated in a general ward without risk of others becoming infected.

The table on p. 804 is based largely on the work of Stanton and Fletcher and shows more clearly than a lengthy description the differences between the *mallei* group and *Pf. whitmori*.

Reference has already been made to the group characteristics of diseases essentially affecting rodents producing acute and serious disease when they accidentally attack man, notably plague, melioidosis and tularæmia. It has even been suggested that the great Plague of Athens which broke out in the second year of the Peloponnesian War (430 B.C.) as recorded by Thucydides, Bk. II, Chaps. 47–54, was not true plague or plague only, for some of the symptoms described and the conditions under which they occurred would equally coincide with both melioidosis and tularæmia. Perhaps it will be of sufficient interest to refer to one or two of these.

CHAPTER 47 :

οὔτε γὰρ ἰατροὶ ἦρκουν τὸ πρῶτον θεραπεύοντες ἀγνοίᾳ, ἀλλ' αὐτοὶ μάλιστα ἔθνησκον ὅσῳ καὶ μάλιστα προσῇεσαν.

A similar disorder is said to have previously smitten many places . . . but there is no record of such a pestilence occurring elsewhere, or of so great a destruction of human life. *For a while, physicians, in ignorance of the nature of the disease, sought to apply remedies ;* but it was in vain and *they themselves were among the first victims, because they oftenest came into contact with it.*

Thucydides himself suffered from it and recovered. He thus describes the symptoms and course.

τοὺς δ'ἄλλους ἀπ' οὐδεμιᾶς προφάσεως ἀλλ' ἐξαίφνης ὑγιεῖς ὄντας πρῶτον μὲν τῆς κεφαλῆς θέρμαι ἰσχυραὶ καὶ τῶν ὀφθαλμῶν ἐρυθήματα καὶ φλόγωσις ἐλάμβανε, καὶ τὰ ἐντὸς ἥ τε φάρυγξ καὶ ἡ γλῶσσα, εὐθὺς αἱματώδη ἦν καὶ πνεῦμα ἄτοπον καὶ δυσῶδες ἠφίει ; ἔπειτα ἐξ αὐτῶν πταρμὸς καὶ βράγχος ἐπεγίγνετο, καὶ ἐν οὐ πολλῷ χρόνῳ κατέβαινεν ἐς τα στήθη ὁ πόνος μετὰ βηχὸς ἰσχυροῦ. καὶ ὁπότε ἐς τὴν καρδίαν στηρίξαι, ἀνέστρεφέ τε αὐτὴν καὶ ἀποκαθάρσεις χολῆς πᾶσαι ὅσαι ὑπὸ ἰατρῶν ὠνομασμέναι εἰσὶν ἐπῇεσαν, καὶ αὗται μετα ταλαιπωρίας μεγάλης. λύγξ τε τοῖς πλείοσιν ἐνέπιπτε κενὴ.

Many who were in perfect health, all in a moment and without any apparent reason, were seized with violent heats in the head and with redness and inflammation of the eyes. Internally, the throat and the tongue were quickly suffused with blood and the breath became unnatural and fetid. There followed sneezing and hoarseness ; in a short time the disorder, accompanied by a violent cough, reached the

chest; then fastening lower down it would move the stomach and bring on all the vomits of bile to which physicians have ever given names; and they were very distressing. An ineffectual retching producing violent convulsions attacked most of the sufferers.

Next, he says:

καὶ τὸ μὲν ἔξωθεν ἁπτομένῳ σῶμα οὔτ' ἄγαν θερμὸν ἦν οὔτε χλωρόν, ἀλλ' ὑπέρυθρον, πελιτνόν, φλυκταίναις μικραῖς καὶ ἕλκεσιν ἐξηνθηκός.

The body externally was not so very hot to the touch. . . . It was of a livid colour inclining to red, and breaking out in pustules and ulcers.

He continues :

They were tormented with increasing thirst, which was not in the least assuaged whether they drank little or much. They could not sleep; a restlessness which was intolerable never left them.

Again :

καὶ τὸ σῶμα, ὅσον περ χρόνον καὶ ἡ νόσος ἀκμάζοι, οὐκ ἐμαραίνετο ἀλλ' ἀντεῖχε παρὰ δόξαν τῇ ταλαιπωρίᾳ, ὥστε ἢ διεφθείροντο οἱ πλεῖστοι ἐναταῖοι καὶ ἑβδομαῖοι ὑπὸ τοῦ ἐντὸς καύματος . . . ἢ εἰ διαφύγοιεν, ἐπι κατιόντος τοῦ νοσήματος ἐς τὴν κοιλίαν καὶ ἑλκώσεώς τε αὐτῇ ἰσχυρᾶς ἐγγιγνομένης καὶ διαρροίας ἅμα ἀκράτου ἐπιπιπτούσης οἱ πολλοὶ ὕστερον δι'αὐτὴν ἀσθενείᾳ ἀπεφθείροντο. διεξῄει γὰρ διὰ παντὸς τοῦ σώματος ἄνωθεν ἀρξάμενον τὸ ἐν τῇ κεφαλῇ πρῶτον ἱδρυθὲν κακόν, καὶ εἴ τις ἐκ τῶν μεγίστων περιγένοιτο, τῶν γε ἀκρωτηρίων ἀντίληψις αὐτοῦ ἐπεσήμαινε· κατέσκηπτε γὰρ ἐς αἰδοῖα καὶ ἐς ἄρχας χεῖρας καὶ πόδας.

The body, instead of wasting away, held out amid these sufferings in a marvellous manner, and either they died on the seventh or ninth day, not of weakness, for their strength was not exhausted, but of internal fever . . . or, if they survived, then the disease descended into the bowels, and there produced violent ulceration ; severe diarrhœa at the same time set in . . . which finally with few exceptions carried them· off. For the disorder which had originally settled in the head passed gradually through the whole body and, if a person got over the worst, would often seize the extremities and leave its mark, attacking the privy parts and the fingers and toes.

Thucydides says later (Chaps. 50-52) :

The birds and animals which feed on human flesh, although so many bodies were lying unburied, either never came near them, or died if they touched them. . . . [This seems a little hyperbolic touch.] Appalling was the rapidity with which men caught the infection, dying like sheep if they attended on one another . . . When they were afraid to visit one another, the sufferers died in their solitude . . . or, if they ventured, they perished, especially those who aspired to heroism. For they went to see their friends without thought of them-

selves, and were ashamed to leave them, even at a time when the very relations of the dying were at last growing weary. . . . More often the sick and the dying were tended by the pitying care of those who recovered, because they knew the course of the disease and were themselves free from apprehension. For no one was ever attacked a second time, or not with a fatal result.

The crowding of the people out of the country into the city aggravated the misery, and the newly-arrived suffered most. For, having no houses of their own, but inhabiting in the height of summer stifling huts, the mortality among them was dreadful. . . . The dead lay as they had died, one upon another.

Nothing, it will be noticed, is mentioned by Thucydides regarding buboes which must have been a most striking symptom, unless the epidemic was plague of the pneumonic type entirely, which is, to say the least, unlikely at the outset ; also in pneumonic plague death takes place usually by the fourth or fifth day, rarely the seventh or ninth which Thucydides speaks of as being the rule in the most acute of the cases described above ; again, relapses, though not common in plague, are of the utmost gravity if they do occur, and not, as he says, " never with a fatal result." In tularæmia second attacks are not recorded. Ulceration of tonsils and mucosæ are common in melioidosis and " bloody tongue and throat " are specially noted by Thucydides ; " pain in the chest, hoarseness and cough " are common to plague, melioidosis and tularæmia ; " severe diarrhœa " is not a frequently seen symptom in plague but a choleraic form of melioidosis was noted early by Stanton ; " pustules and ulcers " are common in melioidosis, but not a feature of plague ; if not fatal, melioidosis commonly affects the limbs with chronic ulceration and discharge, not so plague.

On the other hand, melioidosis may be a new disease in human beings ; otherwise it seems strange that with the intensive bacteriological research of the last fifty years, when bacteria have been suspected, looked for and reported in diseases such as malaria, yellow fever, smallpox, herpes, trachoma, measles, virus diseases in general, its presence should be overlooked in a condition so striking clinically, and an organism, moreover, so readily cultivable.

CHAPTER XVI

DENGUE

The history of dengue as a recognizable disease does not go back very far. Early in the nineteenth century (1827–8) when epidemics were seen in the West Indies, on the coast of the Gulf of Mexico and the Atlantic coast of the southern United States, it was believed to be a new disease. Deeper inquiry, however, revealed outbreaks fifty years before this, but we have not been able to trace any earlier than that at Cairo in 1779. (But see p. 288.)

As with all diseases to which a name is assigned from some prominent symptom and whose cause is unknown, dengue as we call it to-day has had several synonyms. The word·*dengue* is Spanish and means ' affectation,' and *denguero* an affected or dandified person, from the delicate gait assumed or compelled owing to the pain caused by movement. Another Spanish name was *colorado*, or ' blush,' from the character of the early rash. This name cropped up again in 1928 in an outbreak at Andalusia which was again thought to be a new disease. The early cases were mild and convalescence set in in three or four days, but the initial symptoms and the rash were typical of dengue ; as time went on the numbers attacked mounted rapidly and the later cases took on the characters of the classical type of dengue. The French names for dengue in the earlier days were *giraffe* and *bouquet*, the latter implying one with a mincing, coquettish gait, corrupted, as usual, by the British into ' bucket,' thereby destroying the significance of the term. Other, more original English names for the disease were ' break-bone ' or ' break-back ' fever, or the American ' broken-wing ' fever ; the Brazilians called it ' polka fever '—all expressive of the stilted gait. In the Hawaiian islands it was known as *bonon* or sighs, and in Egypt by the non-committal name of *fièvre des dattes*, because it was most frequently seen at the time of date-gathering.

Medical men were more dogmatic and less correct in designating . it *rheumatismus febrilis exanthematicus, scarlatina mitis*, or in more homely English ' insolation fever ' and later ' mild yellow fever.'

The earliest record we have been able to trace is, as mentioned above, that of an outbreak which occurred at Cairo in 1779 and was described by Gaberti under the name *mal de genoux*. The characteristics were fever which lasted for three days, accompanied by pain in the joints, and particularly the knees and the extremities, so severe that movement was very difficult even if possible at all. The onset was sudden and the pains might persist, in milder degree, for three or four weeks. Alexandria was the scene of an outbreak at the same time as Cairo.

We cannot be certain that the condition described by Gaberti was dengue, for no mention is made of the secondary fever and later rash, but these are not always present, as we shall see. As regards the epidemics which were noted in widely separated parts of the globe in the following year, however, there can be no doubt. The condition was described by Bylon, or Boylon, in Batavia, by Persin, a missionary on the Coromandel Coast, and by Rush of Philadelphia. The last describes it clearly under the name ' breakbone fever,' and its epidemic character is noted by Persin who stated that " everyone was attacked." Between 1784 and 1788 Spain suffered and outbreaks were observed in Cadiz and Seville, and in Granada at Santa Fé de Bogotá, the capital.

The next epidemic of any degree of severity was that recorded by Pezet at Lima where but few of the 70,000 inhabitants of the town escaped. During the nineteenth century there were many outbreaks, but only a few call for special remark. In 1824–5 India suffered extensively, as recorded by Hirsch. In May it appeared simultaneously at Gujerat and Rangoon, then at Chittagong, and by July had reached Calcutta and spread along the river by Chinsura, Serampore and Chandernagore, where, it was said, 10,000 natives were ill at one time. In March 1825 it attacked Beshampore, which had not altogether escaped the year before, and thence during the rains along the Valley of the Ganges to Mirzapore. Madras and Pondichery were also attacked. At the time of this outbreak medical men with few exceptions were convinced of the non-communicability of the disease from man to man. Later, in the 1871–2 epidemic, medical opinion had veered round to the opposite extreme and the non-contagionists were decidedly in the minority, and most of the doctors maintained that it was " in the highest degree contagious," in spite of the observations of the very rapid spread of an epidemic and the sudden, almost simultaneous, appearance of the disease in a large part of the population.

In 1827 the West Indies and America, both north and south,

were invaded. The outbreak started, it would seem, in the Virgin Islands and the Danish West Indies—at St. Thomas, with a population of 12,000 " hundreds were attacked daily "—then passed to Santa Cruz and spread over the Greater and Lesser Antilles—St. Kitts, Antigua and the French West Indies, Guadeloupe and Martinique, where " almost the whole population suffered " (Osgood), Barbados, Jamaica, Cuba and Curaçao next, and reaching Pensacola, Florida, early the following year, then attacking Charleston, New Orleans and Vera Cruz and passing thence to Bermuda. Maxwell in 1839, referring to this outbreak as it affected Jamaica, wrote : " Probably never [was] a more general epidemic than this. . . . Almost the whole white and coloured population were sooner or later affected, and very few remained who were not personally acquainted with the dandy fever."

The ensuing thirty years brought reports of outbreaks from almost all over the tropics and subtropics : The Arabian coast (1835), Calcutta (1836), Bermuda (1837), Cairo (1845), Gorée (1845), Rio de Janeiro (1845–9), St. Louis, Senegambia (1848), New Orleans, Mobile, Galveston (Texas), Callao, Lima (1851), Réunion (1851), Tahiti (1852), Cuba (1853), Tripoli (1856), Bermuda (1860) (where, according to Huart, " sporadic cases occur every year and epidemics from time to time "), Canary Islands (1865), Cadiz (1867), Port Said (1868), Zanzibar (1870), Aden, Mecca, Medina, Jedda (1871), Bombay (1871), the first appearance recorded here, and in Dacca (Bengal Presidency) and Madras ; Mauritius (1873) and Amoy (1873).

Of the Rio de Jareiro outbreak in 1845–9 Lallemont writes :

The quickness with which the disease spread [in the summer of 1846–7] was indeed most remarkable. . . . The sickness broke out almost simultaneously in the provincial capital of Raya Grande, opposite our capital, on the other side of the bay. On the *haciende* [plantations, estates] in the neighbourhood whole gangs of negroes fell ill, while in the various mercantile houses there were none of the principals and not always a half-crippled clerk to be found, often for a whole week long. Ships were delayed in loading and unable to put to sea, and even the schools were deserted.

The disease, as has been stated, was first described in Egypt and comparing the accounts of outbreaks there with those in India or America one cannot help noticing that in the former the disease appears to be generally of a milder type than in the latter ; there is less marked rheumatic pain and less liability to relapses. In 1887 there was an epidemic which, from the roseolar eruption

and the free desquamation that followed, was by some confused with scarlet fever.

Towards the end of last century, in 1898, Hardie of Brisbane recorded dengue as being practically a new disease in Queensland. Occasional cases had been seen in the north during the preceding three or four years, but in the summer of 1898 there was a serious outbreak in which about 75 per cent. of the population were attacked. The form was more severe than usually reported from elsewhere, for hæmorrhage occurred from the gums, the nose and stomach ; metrorrhagia and abortion were noted and sequelæ such as pleurisy, jaundice, furunculosis, neuritis and melancholia. Dr. Hare the same year collected accounts of sixty fatal cases, death being ascribed to heart failure and collapse at the crisis.

This, though perhaps the most serious up to that time, was not the first outbreak in Queensland. A study of the literature has shown that it had occurred in 1885 and again in 1891 and 1897, and since then there have been several epidemics which are noteworthy as affording opportunities for experimental work on transmission of infection. Outbreaks occurred in 1904, 1905, 1916, 1917, 1925 and 1926.

Epidemics of dengue resemble one another so closely that it would be waste of time to speak in detail or even to enumerate most of them. Attention, however, may be drawn to two of special importance, the Durban epidemic in 1927 and that of Athens in the same and following years.

In the Durban epidemic of 1927 infection was said to˙ have been carried widely by convalescents, 40,000 cases being known and there must have been many others which were not recognized. The reason given for its spreading so extensively, namely, carriage by convalescents, is probably erroneous, for man is infective only as long as the fever lasts, and rarely longer than the first three days, not in convalescence. The outbreak is noteworthy also for the seriousness of the symptoms in some of the patients—hæmatemesis and melæna, and abscesses were reported as a complication.

The Athens epidemic of 1927–8 was probably the greatest in modern times. During the immediately preceding years the population had greatly increased and there had been a heavy influx of refugees ; sanitary arrangements were bad, breeding-places for Aëdes were abundant and at certain seasons these insects appeared in swarms. Between September 1927 and January 1928 there were 20,000 cases, and by the 4th September, 1928, some 90 per cent. of the population of Athens and the Piræus had been attacked and there had been, it was estimated, 239,000

cases in Athens alone. At first the symptoms were mild, then typical, but from August onwards graver forms occurred and many of the patients died, especially the elderly. Thus at five-day intervals the deaths from dengue in Athens were recorded in August: 1st–5th 9; 6th–10th 18; 11th–15th 27; 16th–20th 92; 21st–25th 141; 26th–30th 103. In Piræus there were 118 deaths in the last ten days of the month.

There had been a severe epidemic in Athens previously in 1883–9, but several clinical differences were remarked. Thus, in the earlier outbreak the temperature had shown an intermission on the third day and a sharp recrudescence twenty-four hours later, but in the 1928 epidemic, though there might be a slight drop of one degree on the third day, the temperature remained continuously high for six days. In the 1928 epidemic hæmorrhages—epistaxis and hæmatemesis—were common, and fatal cases fairly numerous, whereas in the earlier outbreak hæmorrhages were not noted and there were very few deaths. Again, as a rule children are relatively resistant, at all events cases among them are unusual, but in 1928 all ages were attacked and some of the children suffered with vomiting and convulsions.

It may be remarked here in passing that in the Formosa outbreak in 1931 hæmorrhages were a feature and five deaths occurred from intestinal hæmorrhage and hæmatemesis in children between four and ten years of age. In the 1883 epidemic, as is usual, the onset of illness was sudden, abrupt, whereas in 1928 in as large a proportion as 85 per cent. there were premonitory symptoms of headache and anorexia for 24–48 hours.

The fact was noticed that the only area in central Greece free from Aëdes was the only part to escape the epidemic; the Western area of Macedonia also had no Aëdes and no dengue.

In the Western Hemisphere there was a severe epidemic in Miami, Florida, in the summer and autumn of 1934—a warning against allowing *Aëdes ægypti* to breed unchecked. There had been a mild outbreak in New Orleans and Baton Rouge in 1922 and the disease was known to be endemic in the South, but from 1924 onwards only sporadic cases were reported. Then in July 1934 1000 cases occurred unexpectedly near Miami. Within a month another 6000 were attacked and Jacksonville was invaded. Within two months the disease was fairly under control in Florida, but infection had spread into Georgia where several thousands were reported in the three months, September–November, and Alabama had over 1000 cases in October and November. Had

it been yellow fever instead of dengue that the Aëdes was spreading the death-rate would have been appalling. The outbreak was stopped by the advent of cold weather.

Before we pass to consider historically the elucidation of the ætiology of dengue, we may say a few words on allied conditions or other than typical forms of the disease, for the matter is still *sub judice*.

In 1907 Sir Leonard Rogers described *Seven-day Fever*, cases of which he had under observation in Calcutta and he noticed the similarities between it and dengue, but drew a list of distinguishing points. Some were rather differences of degree, but others appeared to be valid points of distinction. Thus, as regards *prevalence*, Seven-day fever occurred annually in sporadic form, whereas dengue appeared in epidemics at long intervals. This is no valid difference, as we have seen at New Orleans and Queensland. Next, as to *race*, Seven-day fever (A) was common in Europeans, but comparatively rare in natives, whereas dengue (B) attacked Europeans and natives equally. Thirdly, *season* ; A occurred in the hot and rainy season only, B might prevail at any time though commonest in the hot months. (We have seen above that cold put a stop to the United States outbreak of 1934.) *Relapses*, he said, were rare in A and did not occur in the same year as the first attack, whereas in B they were very common ; *pains* were, in A, of moderate severity only and rarely affected the joints, were like those of influenza, whereas in B they were the severe ' breakbone ' pains and joint-pain was common, in fact a characteristic feature ; the *fever* in A lasted for five to eight days, with a ' saddle-back ' remission to 100° or 99° F. only, but otherwise continuous in type, whereas in B the primary fever lasted two to three days, was followed by a crisis, then by a short secondary rise, and the type was remittent ; the *pulse* was slow in A, especially in the terminal rise of temperature, whereas in B it was rapid. Finally, in A convalescence was quick and there were no after joint-pains, in B it was tedious and slow and joint-pains might persist for as long as three months.

In 1911 A. Campbell discussed the *Seven-day Fever* of Calcutta anew and came to the conclusion that it was merely a variety of dengue. The *Three-day Fever* of the Punjab he held to be the same as Mediterranean phlebotomus fever, and he advised that until the causal organism or the respective causal organisms were isolated these fevers should be provisionally grouped under ' dengue.' Included in the same group might probably be placed

what is known as *Van der Scheer's Fever,* a fever of five days, liable to attack new-comers, transmissible by injection of serum from patients; the joint-pains were less severe than those of typical dengue. E. P. Snijders in 1928 regarded it as a close ally of dengue—in short as one of the ' dengue group ' and further study by himself and J. E. Dinger led them to the conclusion that the Five-day fever of Van der Scheer and the Seven-day fever of Rogers were both aberrant forms of dengue.

Rather more removed from the typical is the *Twelve-day Fever* of Nigeria reported by L. W. Davies and W. B. Johnson and thought by them to belong to this group. In this, however, the rise of temperature is gradual, there is no remission, the course is longer and the rash more persistent. It would seem to belong rather to the group of typhus fevers such as Megaw has described as occurring in India.

Lastly, there was a condition described by G. Lefrou in 1927, seen by him among Europeans in French West Africa and called *Fièvre rouge congolaise* ; a similar condition was described in 1934 by H. Grizaud in Guadeloupe under the name pseudo-dengue. The characteristics of this were a general morbilliform eruption (the early cases were diagnosed as measles) which disappeared in forty-eight hours without any desquamation. Sporadic cases might be puzzling, for this symptom would appear suddenly after some days of *malaise* and vague limb-pains, but there was no coryza, no sore throat, no Koplik's spots, as in measles ; the long *malaise,* rapid fading of the rash and absence of adenitis differentiated it from German measles. Though the pains were less severe than those of dengue, there was less marked fever and there was nó relapse, and the disease was sporadic rather than epidemic—Lefrou saw twenty cases during 1927—these are not sufficiently valid to warrant its removal from the dengue group and Legendre states firmly his opinion that *fièvre rouge congolaise* is a mild sporadic dengue.

CAUSATION

Dr. Hare of Queensland believed that there was some analogy between dengue and malaria fever because in the blood of thirty or forty cases " Dr. Hunt . . . found actively motile granules mainly in the serum similar to those found in two cases of malaria." Perhaps they were malaria parasites in a dengue patient or perhaps blood platelets showing Brownian movement. The possible ætiological significance of these motile granules does not seem to have been followed up.

The fact that Australia is free from other ' dengue-like ' diseases was utilized for testing the ætiology. Bancroft in 1906 observed that visitors to Brisbane who stayed there during the *day* only would contract it and he therefore suggested that the infection might be conveyed by a day-biting insect, he thought Aëdes (Stegomyia) rather than Culex. Following this up he experimented with the former and produced infection in a volunteer after an incubation period of twelve days. This experiment, however, is open to doubt, for infection by natural means could not be altogether excluded.

Three years before, in 1903, Graham in Beirut had successfully infected volunteers by means of mosquitoes which had previously bitten dengue patients, and in 1907 Ashburn and Craig conveyed the infection by inoculation of blood taken from a dengue patient and filtered through a Berkefeld filter, that is, they showed the cause to be a filter-passer, a virus.

In 1916 J. B. Cleland, B. Bradley and W. McDoneld, also working in Australia, showed that (*Stegomyia fasciata*) *Aëdes ægypti*, after feeding on dengue patients, when taken to Sydney where the disease was not endemic, produced typical attacks in four persons. *Culex quinquefasciatus* (*fatigans*) when tested in the same way proved ineffectual as transmitters. Culex is found all over Australia, but Aëdes is limited in distribution and that distribution coincides with the dengue area, or rather dengue does not extend beyond it. There is no natural dengue south of Newcastle, New South Wales, hence the value of the above experiments in which infected Aëdes brought from Brisbane produced the disease in volunteers in Sydney—an experiment analogous to Manson's employing infected Anopheles from Rome for infecting his son in London (see p. 186). Others before Cleland and his co-workers had carried out experiments to the same end, but as they continued to work in places where dengue was endemic their experiments cannot be held as unexceptionable since natural infection could not be excluded with certainty.

In 1921 L. Couvy during a wide prevalence of dengue in Beirut, Syria, saw, on some half a dozen occasions, scanty spirochætes in the blood during the incubation period, an hour or two before the onset of the fever. He described them as " very fine, with two or three turns." They might be visible for from three to twenty-four hours after the onset. This was known as *Treponema couvyi*. Three years later De Faria claimed to have seen " a leptospira in a case of dengue and proposes the name *Leptospira couvyi* for the organism " (C. M. Wenyon), probably the same as that

described by Couvy. Another worker, in Guayaquil, Carbo-No-boa, the same year inoculated guinea-pigs with the blood and cerebro-spinal fluid of dengue patients and described finding in them a leptospira which he named *L. asthenoalgiæ*. This was found more readily after three centrifugings of the fluid and was probably of the same nature as the *Spirochæta biliohæmoglobinuriæ* of Blanchard and Lefrou associated with blackwater fever (q.v.).

In 1924 J. F. Siler, M. W. Hall and A. P. Hitchens carried out further experimental investigations in Manila on transmission by the agency of insects and were able to confirm the findings of Cleland and Bradley in Australia (1916) and to extend them. They came to the following conclusions:

1. Dengue is transmitted by the bite of infected *Aëdes ægypti*. [They conveyed it thus to 25 out of 42 volunteers.]
2. The patient is infective during the first three days of fever only. With blood taken after that time the results were negative.
3. Eleven days must elapse before a mosquito, *Aëdes ægypti*, which has fed on the blood of an infected person becomes itself infective, but after that it remained so indefinitely. *Culex quinquefasciatus* under similar conditions failed to infect.
4. A certain degree of immunity is conferred by one attack. Between one and four months later about half of those tested were insusceptible and in the remainder the second attack was milder than the first.

Further studies and research carried out in the Philippines in 1928 by J. L. Simmons, J. H. St. John and F. H. K. Reynolds on the virus and its vectors confirmed the previous findings of Ashburn, Craig, Siler, Hall and other American workers, but they found that *Aëdes albopictus* was also a vector, whereas *Culex quinquefasciatus* became an active agent only by direct mechanical transfer. They attempted, but unsuccessfully, to prepare a prophylactic vaccine. Three years later St. John and R. L. Holt, applying Hindle's method for yellow fever vaccine, made a similar preparation from the liver of an infected *Macacus philippinensis*. It did not, however, prove protective though the attacks induced subsequently seemed to them to be of a milder type.

As an outcome of the Athens epidemic experimental work was carried out by C. Blanc and J. Caminopetros on transmission of infection from man to man and to experimental animals. These researches were undertaken in the winter and spring when Aëdes was not present and no cases of dengue appeared. It was found that whole blood, serum, and filtered serum taken from a patient in the first twenty-four hours of illness would convey the disease

and that such serum after being kept in sterile flasks at room temperature for two months was still infective. In one case 3 c.c. diluted, filtered and injected intravenously after being kept for fifty-four days set up the disease in a healthy volunteer, the incubation period being four days. Of two volunteers inoculated with samples of the same blood or serum, one might react with a typical attack, the other showing no reaction, nevertheless four days later the blood of the latter would be infective ; in other words, this person would suffer from, or be infected with, *dengue inapparent*. It was not a case of the virus being carried over because this subject's blood was found not to be infective before the fourth day, nor after the sixth day from the time of inoculation.

J. M. Hoffmann, W. K. Martens and E. P. Snijders in 1932 found that serum remained virulent much longer than fifty-four days. Dried serum was sent to them in Amsterdam from a case of endemic dengue in Java and after being kept for 285 days it produced on injection a typical attack.

It has been said, and repeated, that Graham in 1907 affirmed *C. pipiens* to be a vector of dengue. This is not correct. What Graham did was to collect mosquitoes in the room of a dengue patient at Beirut, convey them to a village some miles away and release them inside the nets of two volunteers. They, and no one else in the village, contracted dengue. In the room where the mosquitoes were collected were both Aëdes (Stegomyia) and Culex. Blanc and Caminopetros carried out transmission work on lines somewhat similar to the experiments of the Australian and American workers. They caught two batches of mosquitoes, one of *C. pipiens* and one of *Aëdes ægypti*, which had been allowed to feed on the same dengue patient, and they were kept for ten days at 22° C. These were then permitted to bite healthy volunteers ; eight out of eleven bitten by Aëdes developed dengue, but none of the eight bitten by Culex. They found that the mosquitoes lost temporarily their infectivity if kept at a temperature below 16° C., but regained it when the temperature was raised again to 22° C. The mosquitoes did not become infective till eight days after feeding on a patient, but, provided the temperature of their surroundings did not fall below 22° C., they retained their infectivity for life. They confirmed the period of chief infectiveness of the patient being the first three days, but found that some degree of infectivity remained as long as the fever lasted.

They further tested the susceptibility of laboratory animals to infection and found the dog and rabbit not susceptible, but that

the monkey was infected with 'inapparent dengue,' the blood being infective but the animal presenting no signs of illness.

The close resemblance in some respects between yellow fever and dengue—tropical diseases with the same vector, the same incubation period, the same period of infectivity and the post-infective immunity—naturally led to the thought that they might be mutually protective and further that the milder disease might protect against the more severe. Blanc, Caminopteros and Giroud tested this in the course of their researches after the Athens epidemic. They injected into a volunteer a potent yellow fever anti-serum into one flank and dengue virus into the other ; after the usual period of incubation dengue declared itself. The same results were obtained if the serum and the virus were mixed together and kept in contact for some hours before being injected ; in other words, anti-yellow fever serum has no action on dengue virus.

The same year Stefanopoulo showed that the serum of patients convalescent from dengue has no action on the virus of yellow fever. There are certain differences between the two viruses as regards filtrability. The virus of yellow fever in human blood is readily filtrable, whereas that in the mosquito is filtrable only with difficulty ; that of dengue is equally filtrable whether in man or mosquito and, according to Blanc and Caminopteros, is recoverable from human blood as long as the fever lasts, whereas in the case of yellow fever it is recoverable only in the first three, possibly four, days.

A study of the distribution shows that if, for generalization, we exclude occasional outbreaks in Philadelphia (as that described by Rush in 1780) and in the south of Spain (as that at Cadiz in 1867), the geographical limits are 32° 47' N. latitude—Charleston in South Carolina and Lodiana, India—and 23° 23' S.—São Paulo, that is tropical and subtropical. History shows it to be in the main a disease of the littoral and in epidemic form is usually restricted to towns, but in small islands the disease may invade the whole, but even then it is generally more marked in the coastal towns. It occurs up to an altitude of 4000 feet (near the equator up to 6000 feet) and may break out at any time if Aëdes is abundant, but is commonest in the autumn ; no race, age or sex immunity is seen. It is probable that in the sporadic form it is often overlooked, or rather evades diagnosis. Even in endemic areas it may die down for a time, perhaps because it spreads so rapidly that

few non-immunes are left, till the number rises again from immigration when it again flares up. Generally speaking, the farther from the equator the less favourable the conditions and so the disease may be absent for years till, as in Greece in 1927, conditions fostering the spread arise and a widespread outbreak rages like a fire embracing a completely non-immune population. On the other hand, in Calcutta for example, some cases are seen every year, especially among newcomers, and from time to time it assumes an epidemic character.

In conclusion attention should be drawn to a plan for International Agreement regarding dengue which was approved at the Session of the Permanent Committee of the Office International d'Hygiène publique in May 1929. The resolutions were :

1. When dengue appears in epidemic form in one of the countries participating in the present agreement, the highest health authority of the country shall notify the other participating countries. It shall keep the Office International d'Hygiène publique informed as to the progress of the epidemic.

2. When an epidemic of dengue is reported in or near a port, the sanitary authority of the port shall recommend to the captains and the ships' doctors the carrying out of a search for and destruction of mosquitoes and their larvæ in all accessible parts of the ships. The physician, or, failing him, the captain should be urged to isolate any dengue patients in places where they cannot be bitten by mosquitoes.

3. Every ship coming from a port where an epidemic of dengue is in progress and arriving at a port where the sanitary authority has reason to fear that the disease may be spread, by reason of the presence of mosquitoes in large numbers likely to transmit it, may be subjected to the following measures :

(a) Enquiries as to the presence on board of any person suffering or having suffered from dengue.

(b) Medical inspection. Any patient who has been ill for less than five days and wishes to land must be isolated in a place protected from mosquitoes, until the expiration of five days from the onset of illness.

(c) Inspection of the ship to ascertain the presence of Aëdes. If reported present, destruction of mosquitoes is to be carried out by [under the direction of] the Port Sanitary Authority.

(d) If considered necessary by the Port Sanitary Authority, disembarked passengers may be kept under surveillance and their baggage confined on board till the expiration of eight days after exposure to risk. [Under what conditions, or for what reasons the Sanitary Authority might deem it necessary to retain the baggage for eight days after disembarking the passengers is not very clear.]

CHAPTER XVII
AMŒBIC DYSENTERY AND HEPATITIS

The claim of amœbic dysentery and hepatitis for inclusion in a work on the history of tropical diseases is open to dispute. The amœbic as well as the bacillary forms occur in temperate climates also. The reason for dealing with the former in this work is that, though it is met with elsewhere than in warm climates, as witness the small outbreak in Chicago in 1926 and the more widespread epidemic of 1933 and its constant presence in New York, it is, nevertheless, much more common in the tropics and subtropics and most of the research upon it has been carried out by men engaged in the study of tropical medicine.

On the other hand, many are inclined to forget that bacillary dysentery is quite common in warm, though possibly more common in temperate, climates and to regard amœbic dysentery as tropical and subtropical and bacillary as non-tropical, a distinction by no means warranted by facts, for on the whole the bacillary form even in the tropics is probably more common than the amœbic.

Prior to Lösch's discovery of an amœba in the stools of dysentery patients in 1875 distinction between the different forms of dysentery was made purely on clinical grounds, hence the earlier history of the affection will necessarily include all forms.

If we were to attempt to give a history of dysentery we should have to go back at least to Hippocratic times; it is mentioned in his Epidemics and in the Aphorisms and he clearly knew a good deal about it and how ordinary diarrhœa might become dysenteric. After him excellent accounts are to be found in the works of Aretæus, Celsus, Archigenes, Galen, Aurelianus, Avicenna and others. In the Plague at Athens during the Peloponnesian War it is almost certain from Thucydides's description that dysentery played no small part. Whether the cases were amœbic or bacillary is now a matter of conjecture, but, judging by evidence available

to us at the present day, we may infer that *epidemic* outbreaks were most probably bacillary. In later times we have an additional guide in the association of the amœbic form with hepatitis and liver abscess, an ætiological connection unsuspected in early days.

From 1840 onwards dysentery was notoriously prevalent on the West Coast of Africa, among Europeans in Senegambia, where it was responsible for nearly one-third of deaths from all causes, and in Sierra Leone, and even earlier, from 1818, it was very marked on the coast of Upper Guinea, and attacked blacks as well as whites in the Gold Coast and on the shores of the Niger Delta. In the latter part of the nineteenth century it prevailed in the Cameroons, in the Gaboon country, still more in Fernando Po and in the Congo. The fatality rate was nearly always recorded as very high, which fact, together with its epidemic character, makes one suspect it to have been bacillary. Thus, on the Guinea Coast among the British troops in 1840–50, according to the Army Medical Reports, the average admissions for dysentery numbered 504 annually and the mortality 41·3 per thousand, while at Cape Coast Castle the fatality rate was 33 per cent. Among the black troops the incidence and mortality were less—309 cases, 25 deaths per mille between 1859 and 1870 on the Gold Coast and at Lagos. Dysentery was endemic also on the East—at Mozambique, Zanzibar, Madagascar, Mauritius and Réunion—but not so severely. Tulloch reporting on the health of the Army in the 'fifties noted that the incidence of bowel complaints serious enough to warrant admission to hospital was 275 per mille ; this figure included cases of dysentery, about three-fifths that on the West Coast, and the mortality rate of 10·6 per mille was less than half. The disease was common in Abyssinia ; among the British troops in the Abyssinian expedition Currie reported in 1867 that 25·7 per thousand of all admissions were on account of diarrhœa and dysentery, and to the west of this country lay Sudan and Nubia which were regarded as some of the worst dysentery regions, extending over the whole of the Upper Nile basin. Franck (quoted by Hirsch) wrote in 1820 : Morbus post pestem maxime in Ægypto timendus est dysenteria, quae huic climati adheret ; and Röser's remark in his work on *Diseases of the East* that " the majority of persons suffering from acute or chronic disease in Egypt die in the end of dysentery which sets in as a complication," shows that more than true dysentery was included, such, for example, as schistosomiasis. Among the French troops in Algeria reports were similar to those of our own on the West Coast—200

or more admissions per mille for this cause, with a fatality rate ranging from 20 to as high as 50 per cent.

To give in any detail the geographical distribution of dysentery in the nineteenth century would mean enumeration of practically all tropical and subtropical countries and many of those in temperate climates—in other words ' diarrhœa and dysentery ' were almost universal. India, Ceylon, the Malay Archipelago and Southern China have been considered the worst regions of dysentery (with Sudan and Nubia not far behind, as stated above), endemic and epidemic, and records from these are legion (Hirsch gives eighty for the period 1828–75). From 1860 to 1872 among British and Sepoy troops in India the rates as given in the Army Medical Reports were Bombay 113·8, Bengal 133·7, Madras 166·3 per mille. Previous records gave, among British regiments, 205 per mille in Bengal, with a fatality rate of only 8 per cent.—this is in favour of the amœbic form. In Ceylon conditions were much worse ; in the eighteen-twenties the mortality among the troops on account of dysentery reached 23 per cent. of the total strength.

In Java, again, the infection, in former days at least, was very serious, causing one-third of the total mortality. Other endemic countries were the West Indies, the Southern United States and South America,

We have stated already that until the last quarter of the nineteenth century, and in some places even later, no distinction was made—none was known—between the amœbic and the bacillary forms of the disease. Without going further into detail we may say that dysentery in epidemic form is usually bacillary and occurs in temperate and tropical climates, especially where the people live amid insanitation or under primitive conditions as exemplified by some native races even to-day. In Europe it is rather an institutional disease, occurring in barracks, prisons, asylums, and spreading also in time of war, as in Gallipoli in the Great European War. It is spread less by direct contagion than indirectly by flies, by contaminated water and food, and by carriers. We shall, however, try to confine ourselves to the amœbic form since it is more limited to warm climates, though not exclusively.

It will be of interest, historically, to trace briefly the development of the separation of dysentery, first into two main forms, later into more than two. Until after the middle of last century diarrhœa and dysentery were always spoken of together and it was generally held that diarrhœa, if neglected, developed into

dysentery. It was noted that endemic dysentery was commonest in the tropics and adjacent-subtropics ; in regions more remote sporadic cases and epidemic outbreaks were more common. In endemic equatorial regions, cases were observed at all times, but usually less frequently in the cool season, the worst being not that of maximum temperature but the end of the rainy and beginning of the dry season—the time of great fluctuations of temperature, hot days and cold nights. Epidemics in temperate climates are more common at the end of summer and in the early autumn. This has been noted in India, in Egypt, in Peru, Barbados and elsewhere.

For a time the chase was diverted by the observation that states of the soil and places where general conditions were favourable to malaria were also places where dysentery was endemic, as the slopes of the Himalayas, Java, Ceylon, Martinique, and places where the soil was damp and marshy. It was but a short step from this—an erroneous side-slip—to speak of dysentery as a malarial disease. Thus Annesley, writing in 1841 of India, says :

> Of dysentery as well as of fevers it may be confidently stated that all situations productive of terrestrial emanations or malaria, and which furnish exhalations from the decay of animal or vegetable productions, under the operation of a moist and hot state of the atmosphere will always occasion dysentery in the predisposed subject.

Lenoir has spoken in similar terms of Cochin China ; Lemprière, Mason and Hunter of the West Indies ; Sigaud of Brazil ; Perier and others of Algiers, and Griesinger of Egypt.

Looking back from our higher vantage-point we see the trap into which they fell, namely, interpreting the co-endemicity of dysentery and malaria as evidence of identity of cause. The observers saw too much and they based their dictum on a survey of large tracts of country, whereas had they studied smaller areas and compared them, they would have seen that within the larger expanse were several districts with widely differing soils and climates and that areas of malaria and of dysentery did not correspond so closely as they imagined. Moreover, in some parts where malaria is most severely endemic dysentery occurs but little, as Gujerat, Puchmurri, Amboina and Mayotte, one of the Comoro Islands of which Dutroulau wrote :

> L'endémie paludéenne absorbe toute la pathologie dans ce climat ; elle est hors de proportion avec toutes les autres maladies réunies . . . La dysentérie endémique est à peu près inconnue à Mayotte. Pendant les plus mauvaises années, qui ont été les premières de l'occupation, on n'a observé que quelques cas sporadiques de cette maladie.

Again, Grande-Terre in Guadeloupe is highly malarious, nevertheless dysentery patients used to go there to recuperate.

The reverse also holds good ; there are centres of severe dysentery which are free or almost free from malaria, as Balgâm, Meerut, Ferozepore, Réunion and Mauritius—in the last, as we have seen, there was no malaria until 1866—Basse-Terre and Barbados. There is no need to labour the point, but one quotation, the words of Beauchef in 1865, sums up the matter as exemplified in Cochin-China : " Des localités où les fièvres intermittents sont d'une fréquence et d'une gravité extrêmes sont peu visitées par la dysentérie ; d'autres réciproquement, où la dysentérie exerce ses ravages, sont exempte de fièvre."

The connection between dysentery and impure drinking water is so obvious and has been noted so often that there is no need to dwell on this aspect of the subject.

Though the various forms of dysentery were in those days thought to be due to one cause, those engaged in studying its pathology noticed the varying conditions present and the different characters of the lesions found post mortem. Some showed ' follicular ulcers,' others ' catarrh ' of large stretches of the mucosa, others again ' diphtheritic exudation ' and so on. These findings were probably the first pointers to a varied ætiology and the question began to be asked, " Is there only one dysentery virus ? " The condition was observed to be infective—the communicability of dysentery had been noted early in the seventeenth century, and probably before ; it is certainly mentioned in Sennert's treatise of 1626—and now began an earnest search for parasites. In 1869 Hallier found spores of a fungus, hitherto undescribed, in the intestinal contents ; Basch in the same year, after carrying out post-mortem examinations of patients dying of dysentery during the war in Mexico, reported that he found micrococci and mycelia in the villi of the small intestine and in the crypts of Lieberkühn in the large.

In 1875 came the first true light—the finding by Lösch of amœbæ and the history of dysentery enters on another stage. Before treating consecutively and in detail this stage we must retrace our steps a little. In the mid-years of the nineteenth century Sir James Ranald Martin, a man with wide Indian experience, wrote on dysentery and remarked that next to malarious fevers bowel complaints were the most prevalent diseases, while the danger to health and life from the latter he regarded as even greater than that from fevers. From his description Martin, as

one would expect, mixes amœbic and bacillary, but the former would seem to be the more common in his experience, for he notes the frequency of liver abscess, and in a considerable number scurvy would seem to have been present also. He states that in one campaign he saw forty die in a single night, the symptoms being swollen, loose and livid gums, with ulcerated and sloughing edges, fetid breath, pain and hard swellings in the calves, purple discoloration of the skin of the lower extremities, œdematous swelling of the feet and legs, anasarca—ascites and hydrothorax—and he calls the condition 'scorbutic dysentery.'

Also, where there was neglect to obtain proper food, when local sanitary surroundings were bad and the air foul, the soldiers suffered from a deadly dysentery accompanied by sanguineous discharges from the gums, nose, fauces and bowels. In these the liberal use of pure lime-juice, vegetables, fruits and potatoes was called for.

That there were differences of form of dysentery he was well aware, for he compares the disease in India with that seen in England and quotes Dr. Baly as saying that " In the Millbank Prison out of many hundreds of cases which occurred during seven years not one has been complicated with hepatic abscess " and he cautiously adds :

These facts would lead to the conclusion that a foreign climate mainly, and its unnatural influences, and more particularly heat and malaria, produce the difference of result as respects British subjects ; but it is most difficult here, as in other diseases, to determine what is cause and what coincidence.

In his day and in the half-century preceding it the disease was very fatal in India. He quotes the figures of admissions and deaths at the European General Hospital, Calcutta, in 1797–9, and states that of 238 cases of dysentery treated 127 died, a fatality rate of 51·5 per cent.

Chisholm also recognized two kinds of dysentery, but reading his description one is led to think that in each of the two he was placing a mixture of cases. He divides them into Sporadic or Idiopathic and a form ' often Epidemic.' The Sporadic arises, he says, from suppressed perspiration and irregularities in clothing and diet. He notes the passage of blood and mucus separately—symptoms of the bacillary form—and records an instance of the danger of neglecting to take precautions to prevent spread. In the siege of Savanna, Georgia, in 1779, there were 250 such of " yellow remittent fever and (idiopathic) dysentery " confined to two ships of about 300 tons each, foul and ill-ventilated. There

being too few not attacked to attend to the wants of the sick the stools were left unmoved. More than two-thirds perished and later, when the survivors were admitted to hospital, they brought the contagion with them and spread it there. He describes the post-mortem appearance of the bowel ; the " large intestine showed gangrenous blotches and tubercular excrescences (from exudation of lymph) " and portions of gangrenous bowel might be passed *per anum*. All this would seem to point to bacillary dysentery, but he notes that if the case was recent benefit followed the taking of ipecacuanha, which would be in favour of the amœbic origin.

His second form was " more dangerous, prevailed during the hot and rainy season, produced by marsh miasmata " and often epidemic. Moreover, he calls this form ' hepatic dysentery ' ; the stools were frequent and of a fluid consistency ' like washings of raw meat.' If neglected, the attack might prove fatal in six, ten, or, at most, twenty-four hours. The liver was found enlarged, inflamed and ' particularly suppurated ' or ' like rotten cork ' ; the intestinal canal was more or less extensively inflamed and " more especially the smaller intestines."

It is difficult to place this condition ; amœbic dysentery does not kill in " six, ten, or at most twenty-four hours," nor does it in that time produce a widespread hepatitis, whereas multiple minute pus collections would be more likely to occur in bacillary dysentery.

Chisholm also describes in considerable detail forms of hepatitis, some at least he seems to link up with enteritis, or diarrhœa, but his accounts are not sufficiently clear to make this certain, and we need not, therefore, enter into this in any detail ourselves. He mentions *acute hepatitis*, which he thinks·was not seen before 1770, with sudden onset and death in three to five days from ' gangrene of the liver ' and abscess. Also what he calls *anomalous hepatitis* which he saw in Grenada in 1785 and after. This may affect whites as well as blacks, but the latter seemed to be more liable, all ages and both sexes suffered, but more those between 8 and 25 years of age, because, he states, they are more exposed to cold dews at night and northerly winds during the day, that is adolescents and young adults worked longer hours in the open. It was, apparently, infective, for if one parent was attacked all the members of the family might suffer ; he mentions the case of a woman being ill with this condition and all the domestics and several of the field negroes who visited her " received the infection." It is difficult now to say what the condition was or its cause.

The symptoms he records were headache, dyspnœa, epigastric pain without vomiting, pulse 70–80 per minute ; later the pulse rate increases up to 120 and there are sweating, bronzing of the face, cough, and death in coma ; the fatality rate is about one in six.

He describes also a *chronic hepatitis* the symptoms of which were those of amœbiasis going on to abscess, with shoulder pain, pain in the liver region aggravated by attempts to lie on the left side. This he treated with nitro-hydrochloric acid or chlorine baths.

In connection with these forms of hepatitis Chisholm speaks of " enteritis with a tendency to gangrene " which may have been dysenteric, for his ' enteritis ' includes colitis. He does not seem, however, to be clear about the condition in his own mind, for he states as cause sudden chill as from throwing off clothes when one is hot, or a draught of cold water drunk when the subject is heated causing " instantaneous gangrene in the viscera and fatal gastric syncope."

Hepatic abscess was a very fatal complication in those days ; thus of fifty-nine cases reported in Madras in 1844 forty died, and in another analysis four died out of every five.

As long ago as 1845 Budd, in his work on *Diseases of the Liver*, laid stress on the fact that metastatic infarcts in the liver might follow ulceration or gangrene of the intestine and from that evolved the theory that *in the tropics the endemic prevalence of abscess of the liver is causally connected with the dysentery that is likewise endemic in those regions*. Hirsch remarks anent this theory that, though having a scanty foundation, it was received with applause, but that " neither statistics nor the due consideration of other matters of experience in the endemic hepatitis of the tropics are in its favour." He quotes figures which in total amount to 2377 fatal cases of dysentery in which at autopsy 457 had also abscess of the liver, or 19·2 per cent. I have not compared these with more modern figures, but at a casual estimation they strike one as constituting an unduly high proportion. When we remember that tropical abscess of the liver is a complication or, more often, a fairly late sequela of amœbic dysentery and that only a certain proportion of cases of dysentery are due to amœba, to find nearly one in five showing a concomitant hepatic abscess is beyond the experience of most of those who have practised in the tropics. Hirsch adds : " We are not told how many of the cases had the two affections coexisting but independent, or in how many of them the hepatitis had preceded the dysentery." With our modern knowledge this is interpreted as meaning that hepatic emboli may occur early before the signs of acute dysentery have

declared themselves, or where the diarrhœa is of such a character —either in kind or in degree—as not to be interpreted as dysentery. More than one writer of repute in those days, Annesley and Geddes for example, have declared that " abscess of the liver is a frequent occasion of dysentery." As further contrary evidence the epidemic of dysentery among British troops at Wallajabad in 1807 is adduced. This was a severe epidemic with high fatality and the report of it published in 1809 states :

From an examination of almost all the men in the regiment who have died of dysentery, it can hardly be said that the disease is connected with visceral derangement, for in only one case was the liver found suppurated.

The only comment we can make at this long interval of a century and a quarter after the event is that epidemic dysentery is not usually amœbic but bacillary, and it is the former which is associated with tropical abscess of the liver. Other evidence is brought forward of countries outside the tropics where " severe epidemics of dysentery are far from uncommon, although abscess of the liver . . . counts as one of the rarest of maladies, and as a sequel of dysentery rarer still." Figures from the Military Hospital at Nancy and the Pathological Institute of Prague are given, showing, as would be a fair inference with our modern knowledge, that the form of dysentery was the bacillary. Hirsch concludes : .

Although abscess of the liver is a rather common complication of dysentery, and the two affections may in many cases be even causally related to each other, we are by no means warranted in concluding . . . that dysentery is the real occasion of hepatic abscess being endemic in the tropics.

There are, of course, other causes, several other causes, of hepatitis and abscess of the liver in the tropics, but the association of the solitary abscess with a history of a previous attack of dysentery, the finding of *Entamœba histolytica* in the discharge of otherwise sterile pus, the results of treatment with emetine in cases submitted, or not, to open operation, has in the half-century since the above was written, narrowed the question by eliminating dysenteries other than amœbic and the ætiological connection of amœbic dysentery with tropical abscess of the liver is definitely established.

Robert Jackson remarks that dysentery was one of the most important of the diseases affecting the troops particularly in the West Indies, where, in some of the islands, it amounts to one-half, even to more than half of all the forms of acute disease which appear in the hospital return of sick. It is more dangerous

in itself ; more fatal, in fact, among the military in the West Indies, either primarily or secondarily, than any other, the concentrated fever, as incident to strangers, excepted.

By this he probably means yellow fever. He does not mention hepatitis specifically in this connection, so we cannot tell which form of dysentery he refers to. So far as the author's experience of nine years in the West Indies goes the commoner form is bacillary.

To speculate further on the varieties of dysentery prior to the discovery of the amœba would be a mere ploughing of the sand. Our concern being amœbic dysentery we pass on to the history of the *E. histolytica*.

This amœba was discovered in 1875 by Lösch in the stools of a Russian peasant, named Markoff, who had come from Archangel to St. Petersburg looking for work. He fell ill with dysentery and after five months in hospital died of pneumonia. Lösch described the amœbæ, their size, appearance and character of the nucleus, from which it is clear that he was describing the true protozoon of dysentery. Though he was able to infect a dog with fresh stools from the patient he did not regard it as the actual cause of the disease but, as did others after him, believed that it prevented the healing of dysenteric ulcers. He named the protozoon *Amœba coli.*

This was not the first time that amœbæ had been found in man. Clifford Dobell ("Amœbæ living in Man," *Med. Res. Council Rep.,* 1919) states that the first was discovered by Gros in Russia in 1849, later known as *E. gingivalis.* Steinberg in 1862 rediscovered this and in the second decade of the present century it was thought by Smith, Barrett and others to be the cause of pyorrhœa alveolaris, but further study showed it to be a harmless commensal. In 1860 Lambl reported the finding of amœbæ in the intestine of a child dying from enteritis, but Leuckart in 1863 stated that in his opinion they were degenerating forms of *Trichomonas hominis* and with this Dobell agrees. It was probably Lewis in India in 1870 who first discovered intestinal amœbæ and this was confirmed by Cunningham the following year. Both saw them when carrying out investigations into cholera, and it is probable that what they saw was that now known as *E. coli.*

After Lösch's discovery discussions arose as to whether the amœbæ were the actual cause of dysentery and the question remained long unanswered, the reason being (says Dobell) first, that amœbæ form a group of which some members only are pathogenic ; second, that dysentery also comprises a group of diseases,

some due to bacteria, another to amœba. Italians next took up the investigation, the most noteworthy being Grassi (1879–88), Calandruccio (1890), Celli and Fiocca (1894) and Casagrandi and Barbagallo (1895), but they also failed to discover that more than one form occurs in man and since they were dealing mainly, if not solely, with what now goes by the name *E. coli*, they concluded that all intestinal amœbæ were harmless.

The next step was the finding by Koch in 1883 of entamœbæ in sections of dysenteric ulcers—he, with Gaffky, recorded this in 1887—and in one case in the wall of a liver abscess. In 1886 Kartulis in Egypt reported that he had found them in 150 cases of dysentery and in twelve of them in sections of the ulcers ; the following year he saw them in the pus of a liver abscess (he recorded them in a brain abscess seventeen years later). The year 1887 is therefore a notable one in the history of dysentery, for Kartulis's findings and their confirmation by Koch and Gaffky and for the proof of what had long been observed clinically by medical men in India, namely the close association between ' tropical dysentery ' and ' tropical abscess of the liver.' The same year Hlava at Prague experimentally produced dysentery in cats. In 1899, four years after William Osler in America had confirmed the presence of amœbæ in liver pus, Kruse and Pasquale produced dysentery in cats by rectal injection of liver pus. The same year Quincke and Roos, working in Kiel, described the cysts and demonstrated that cats could be infected either by swallowing the cysts or by injection of vegetative forms *per anum*, and concluded that man became infected by ingestion of the cysts. They also distinguished the dysentery amœba from the more slowly moving *E. coli*. Other workers of note in the early 'nineties were Councilman and Lafleur (1891) and Kovács (1892). The former described the lesions in the bowel and are responsible for naming the disease " amœbic dysentery." The position at this time was that there was more than one species of intestinal amœba and that one of these was a cause of dysentery, though the epidemic form was usually bacterial in origin. The ensuing ten or twelve years were, as Dobell describes it, a period of chaos due, he believes, to Schaudinn's work—work remarkably full of errors considering it was by a protozoologist of high repute—and to the thesis of Musgrave and Clegg in the Philippines that " all amœbas are or may become pathogenic." Thus, as late as 1906 they seem to have considered that there was but a single species, attaching no importance to morphological differences. They did good service, however, in devising or improving methods of cultivating *free-living*

amœbæ and it was they who introduced the useful term 'amœbiasis.' Actual cultivation of the entamœba of dysentery was not accomplished until W. C. Boeck and J. Drbohlav succeeded in — 1924 in doing so with a medium of coagulated egg-albumen covered with one part human serum to eight parts of Locke's solution—changed later to one in seven inactivated human or rabbit's serum. In 1901 Harris infected puppies with amœbæ from a human case and two of his animals later developed liver abscess. In 1903 Huber studied a case of amœbic dysentery, saw the vegetative and cystic forms and infected cats, as Quincke and Roos had done, by administration of cysts *per os* and amœbæ *per anum*. He described the cysts with nuclei up to four in number and distinguished them from those of *E. coli*. Though Huber reported his findings to Schaudinn, they seem to have been forgotten or shelved till they were rediscovered by Viereck and by Hartmann in 1907 and again by Elmassian in 1909 and named respectively *E. tetragena*, *E. africana* and *E. minuta*. The confusion, however, was not cleared until Walker in 1911 and Sellards in 1913 published an account of their investigations into the development of the entamœba and showed that *E. tetragena* and *E. minuta* were identical and synonyms of *E. histolytica*. Walker distinguished the free-living from the parasitic amœbæ and stated that the forms which had been cultivated were the free-living, that these as cysts had passed unchanged through the bowel, and that there were two species of true parasitic amœbæ, *E. coli* and *E. histolytica*, the latter only being pathogenic ; further that the former gave rise to octonucleated cysts, the latter to quadrinucleate and that man became infected by these cysts. The paper published under the joint authorship of E. L. Walker and A. W. Sellards clarified the whole question. They based their conclusions on carefully carried out experiments. First, they fed volunteers from among the Filipino inmates of Bilibid Prison at Manila with cultures of saprophytic amœbæ—not entamœbæ—such as occur in water and on vegetables, and considered by Musgrave and Clegg to be pathogenic for man. On ten volunteers twenty experiments were made, using mainly the encysted forms of the amœbæ. In no instance did dysentery result. Next, they fed twenty men who were free from *E. coli*, with cysts of this amœba and in seventeen of them *E. coli* in vegetative form was observed in one to eleven days, but, again, none of the subjects showed any dysenteric symptoms. Thirdly, they fed twenty men with *E. histolytica* (and some *E. tetragena*). Those fed with the former passed also the latter, proving their identity. Seventeen of the twenty were

parasitized by the first feed and one more after three feeds. Four of the eighteen parasitized developed dysentery.

Studying the life-history of the entamœba they found it to be similar to that of *E. ranarum* which had previously been worked out by Dobell. The large vegetative amœboid form produces under certain conditions into which we need not enter here a smaller form which gets rid of any food particles contained and then encysts, this smaller form is therefore denominated ' pre-cystic.'

It was Walker also who made the important discovery of the ' carrier ' state in connection with this disease and subsequently Wenyon, Darling (1912) and James (1914) filled in various details.

Amœbic dysentery is now known to have a wide area of distribution—Egypt, Northern Africa, West Africa; France, Germany, Denmark, Italy, the United States, Canada and Australia. Dobell found cysts in a proportion of healthy persons in temperate climates, 7–10 per cent. among the working classes in the north of England who had never been out of the country ; as many as 35–54 per cent. were passing *E. coli* cysts. The proportion was higher among the miners. Occasionally indigenous cases of dysentery were met with among them. Later, in 1924 A. M. Smith examined numbers of apparently healthy persons in Great Britain who had never been out of the country and found from 1·5 to 5·6 per cent. to be cyst-passers, and in two series of inmates in asylums 4·2 and 9·7 per cent. It is known, however, that such carriers are not really healthy ; they are liable to recurrent attacks of diarrhœa, abdominal pain and other symptoms. E. Brumpt, it must be remembered, records *E. dispar* as having a quadrinucleate cyst-form, but differing pathologically from *E. histolytica* in not giving rise to fatal dysentery when injected intrarectally into kittens. He finds this harmless form frequently in human subjects in temperate climates and thus explains the frequency of quadrinucleate cysts in healthy persons in England and France. C. M. Wenyon regards *E. dispar* as *E. histolytica*, in fact gives it as a synonym and does not believe that such physiological data are valid for distinguishing species. Scott found in Jamaica, in apparently healthy persons, some who were passing cysts of *E. histolytica*, though the amœbic form of dysentery is very uncommon there.

E. Martin in 1908 and Vincent the following year spoke of carriers—*les porteurs d'amibes*—but not knowing the life-history of the parasite they regarded the ' carrying ' as similar to that of bacteria, whereas Walker's term meant ' cyst-passers.' Walker

divided such persons into 'contact carriers' who have never suffered from dysentery and 'convalescent carriers' who have, from the clinical point of view, recovered from an attack but continue to pass the cysts and are, therefore, a menace to others. The former have not been ill, the latter have been and may be again.

The entamœba as the cause of dysentery was not accepted without opposition. Thus, A. R. S. Anderson of Port Blair, Andaman Islands, writing in 1908, stated that though more than half his dysentery patients passed amœbæ in their stools, nearly one-third of non-dysenteric subjects did so too, and the amœbæ in the latter were indistinguishable from those in the former which were, he says, undoubtedly *E. histolytica*. He maintained, therefore, that the protozoon was a harmless commensal. He went further and, seeing that less than 1 per mille developed liver abscess, affirmed that *E. histolytica* was not the cause of abscess of the liver. Even later than this physicians failed to differentiate *E. coli* from *E. histolytica*; in 1910 Allen supported Musgrave and Clegg and held, in opposition to Schaudinn, that all amœbæ constantly found in the stools were pathogenic and that anyone continuing to pass them would sooner or later show signs of amœbiasis. Two years later W. M. James again stressed the fact that confusion still existed between the pathogenic *histolytica* and the harmless *coli*, and again defined the differences clearly, showing further that *E. histolytica* and *E. tetragena* were identical.

In following the sequence of events succeeding on Lösch's discovery in 1875 we have had to omit certain other discoveries to which we must return. The same year that Lösch found the amœba Treille reported the presence of *Paramœcium coli* in six out of nine cases of dysentery whose stools contained blood; he did not find them if blood was absent. In 1881 Moty reported the presence of monads, vibrios and other parasites, but guardedly acknowledged that he did not think they were of ætiological significance. Mackie the following year affirmed that the cause of a certain type of dysentery in Egypt was *Distoma hœmatobium*. He was doubtless referring to *Schistosoma mansoni*, for *S. hœmatobium* (*Bilharzia hœmatobia*), the urinary form and *S. mansoni*, the rectal form were for long confused. Griesinger, however, had forestalled him in this by several years.

From the observations of Quincke, Roos, Walker and Sellards there followed logically consideration of the mode of transmission

and the natural conjecture was that infection took place *per os* in food or drink, the parasite adhering to ·fruit or vegetables, or living free in water.

TREATMENT

From the historical point of view the treatment of dysentery is the history of the use of ipecacuanha. As a remedy this is first mentioned in 1625 in Purchas's *Pilgrimes* and in 1680 was used as a secret remedy by Helvetius, being aided financially by Louis XIV, the same who subsidized and purchased Talbor's secret remedy, cinchona. Ipecacuanha had been brought to Europe from Brazil in 1658 and from 1660 onwards employed in India in small doses for the treatment of dysentery patients. Scott-Docker is sometimes said to have been the first to introduce its use in larger doses in 1848 in Mauritius, but Parkes in India was giving doses of 30–60 grains in 1846. In 1855 ipecacuanha was being spoken of as a new discovery for treatment of dysentery, but it had been known for ' well over a century.' A writer in 1837 gives details of its method of administration :

A sinapism to cover the abdomen and immediately after this a drachm dose of laudanum. Half an hour after, when the irritability of the stomach has been diminished, the ipecacuanha is administered, generally in a draught, sometimes in pill or bolus, while a semirecumbent posture is steadily maintained.

In one regiment 104 cases of dysentery were admitted to hospital ; sixty-eight were treated ' in the ordinary way ' [this is not detailed] and six died, 8·8 per cent. " Of another party numbering fifty-nine treated with large doses of ipecacuanha, all recovered." The doses given were 10–90 grains, rarely less than 20 grains, and usually one scruple to half a drachm.

Hospel, a French physician, noted in 1852, as a result of his observations on the use of ipecacuanha in cases of liver abscess in the army in Algeria, that the drug acted by reducing hepatic congestion in two ways ; one by drawing blood from the liver to the stomach, and the other through the muscular contractions due to the vomiting. Delioux and Savignac during the next decade· carried out chemical experiments clinically on patients in the Naval Hospitals of Rochefort and Toulon and came to the conclusion that ipecacuanha was " a specific for dysentery as quinine for malaria," and that the vomiting was· not a good but a bad element, the beneficial effect being due to the ipecacuanha *absorbed*.

In 1886 Norman Chevers and Maclean were giving it in cases

of hepatitis, empirically to prevent development of abscess, but another twenty years passed before the empiricism changed to rationalism when Rogers showed that hepatitis and hepatic abscess were secondary to amœbic dysentery.

Liver abscess, its pathology and connection with amœbiasis was intensively studied by Rogers during his twenty years as pathologist to the Calcutta Medical College Hospital and he made it the subject of his Lettsomian lectures in 1922. Up to the early years of the present century Andrew Duncan, at the London School of Tropical Medicine, had maintained that dysentery and tropical abscess of the liver were unrelated, but in 1902 Rogers announced that amœbæ were to be found in the abscess wall and that a very large proportion, 80–90 per cent., of tropical liver abscesses were primarily free from bacterial invasion, infection occurring subsequent to operation, with a consequent fatality rate of 50–60 per cent. Till then the abscess was believed to be due to septic pylephlebitis. It was largely on this account that he advocated aspiration in preference to open operation. To Rogers is also due our early knowledge of the pathogeny ; he pointed out that from the main abscess cavity extension took place along the veins, whereby small concentric circles of liver tissue broke down to form a large ragged-walled acute amœbic abscess.

The stages through which the treatment of tropical (amœbic) liver abscess passed may be mentioned here to save our having to return to the subject. Drug treatment of dysentery and its associated employment in hepatitis will be dealt with later. In the pre-anæsthetic and pre-antiseptic days abscesses were left till they pointed, when they were opened and drained and the fatality rate was nearly 100 per cent., though at times cases were reported where the pus was ' resorbed.' H. Blanc of Bombay recorded in the *Lancet* of 1861 four cases where resorption followed the local application of Vienna Paste [Pasta potassæ et calcis] an escharotic, and Saint-Vel, who practised in the Antilles in 1868, recorded a similar case in a negress. Morehead, Dutroulau, Vauvray, Bérenger-Féraud and others have also recorded cases of spontaneous cure of liver abscess by resorption.

When antiseptics came into use and anæsthesia permitted more leisurely operation, open operation and drainage were still the mode of procedure, but the fatality rate, though less, was still very high, from 60–80 per cent. In 1883 Manson introduced the operation by means of trocar and cannula and the prospects greatly improved, though it is probable that several deaths occurred from hæmorrhage, if the operation was performed in the pre-

suppurative stage of engorgement. In 1909 still better results were obtained by the use of ipecacuanha either before or after operation ; sometimes it was given at both times. Though at this time employed rationally (except that the mode of action of ipecacuanha was not known) this combined treatment was not really new. Maclean, nearly forty years before, in 1871 advocated giving ipecacuanha internally and evacuation of pus by means of a syringe. Next, Rogers advised the use of emetine in all cases of liver abscess, combined, if the abscess was large, with simple aspiration. In a series of cases of liver abscess in Europeans analysed by Rogers in Calcutta 20 per cent. had opened through the lungs—usually the right, as would be expected—and nearly half (46 per cent.) of the patients died. Later, in the nineteen-twenties, owing to early recognition of the liver condition, even in the pre-suppurative stage, and the administration of emetine, opening into the lung was uncommon and death rare.

D. M. Ross had tried ipecacuanha in the dysentery of Jamaican negroes and was disappointed with the result and he obtained more success with sulphate of magnesium and dilute sulphuric acid. [We have stated above that amoebic dysentery is rare in Jamaica, and this fact lends support to the conclusion that the dysentery in this island is mainly bacillary.]

In the South African War, 1899–1902, where dysentery was common and fatal, it was the author's experience that ipecacuanha was useless except in cases occurring among soldiers brought over from India ; the others responded much better to concentrated salines. At the time this was not explained, but in the light of subsequent discoveries it is clear that the epidemic cases were probably bacillary, as is usual in military campaigns, whereas the Indian cases were probably relapses of the amoebic form contracted in that country.

In 1817 Pelletier isolated emetine from ipecacuanha, and when ipecacuanha came to be used as the routine treatment for dysentery, the difficulties of its administration, at least of its being retained, were increased owing to its emetic action. Hence for a time this alkaloid was separated and *ipecacuanha sine emetine* was used, but proved very disappointing. Nearly a hundred years passed after Pelletier's work before E. B. Vedder, in 1911, demonstrated the lethal action of emetine on amoebæ and that the efficacy of ipecacuanha depended on the amount of emetine contained, the Brazilian root containing most. In the ensuing three years Rogers standardized its use in amoebic dysentery. As the usual dose of Pulvis ipecacuanhæ was 30–60 grains and as 90

grains of the powder contains 1 grain of emetine—the usual daily dose—the advantage of the latter is obvious, and still more so with the discovery of the efficacy of its administration by hypodermic injection since the dose could be accurately standardized and there was no risk of its rejection by vomiting. It is a widely held belief that the delay in employing emetine, which had been discovered and isolated early in the preceding century, was due to the fact that ipecacuanha was an emetic and that its beneficial effects were largely ascribable to this action.

In 1912 Rogers reported that the soluble salts of emetine could be safely injected subcutaneously without causing nausea and he obtained good results in acute and chronic amœbic dysentery and in amœbic hepatitis from administration in this form and by this route. Further he recorded cases of liver abscess treated by aspiration and injection of emetine hydrochloride into the abscess cavity (without drainage) as has been stated above. He published an instructive comparison in the *Therapeutic Gazette* and in the *Indian Medical Gazette* of 1912 from which the following is extracted : Of thirty patients treated with ipecacuanha eleven died, two were taken away in a moribund state by friends ; in thirteen the stools became normal in 11·4 days (average) and the patients left hospital after 16·4 days ; one improved greatly but did not recover completely, three showed no improvement. In contrast with these twenty-six were given emetine. Of these two died within two days of admission, two recovered from the dysentery but succumbed to other conditions, twenty-two were cured ; their stools became normal in 2·3 days and they were discharged from hospital in 7·2 days. The figures speak for themselves. The average doses needed for cure were, of ipecacuanha 406 grains, of emetine 2 grains.

In a recent article (*Marseille Médicale*, September 1937) Huard claims that Rogers had been forestalled by more than a quarter of a century by certain French physicians. He states that Dr. J. J. Florence, after an interview with Rogers in 1914, wrote regarding the introduction of emetine :

Ce serait un erreur de laisser la gloire de cette thérapeutique à l'illustre médicin anglais. . . . Nous devons, par respect pour la mémoire de notre père, le docteur Florence, de Perpignon, rappeler que déjà, en 1882, frappé des inconvénients de l'ipéca à la brésilienne, ce practicien employait l'émétine en injections hypodermiques.

Again, in *Dictionnaire Dechambre*, published in 1887, Labbée in an article " Emétine," wrote :

L'émétine est le principe actif de l'ipéca et peut le remplacer dans toutes ses applications. Toutefois, l'avantage d'une pareille substitution

peut être contestée. L'action émétique a surtout été recherchée. On la détermine en administrant la substance médicamenteuse en injection sous-cutanée ou en ingestion.

Coming to more recent times, the Great European War. In 1916–17 amœbic dysentery was prevalent in Gallipoli and in Egypt, and emetine maintained its reputation, but its mode of action remained obscure and work of a research nature was undertaken to elucidate this. Extracts were made from the stools of patients receiving ipecacuanha but were found to have no action on amœbæ ; in other words the stools did not contain any of the amœbicidal constituents of the drug. It was thought that it acted only on amœbæ in the tissues and when they had been destroyed the lesions healed naturally. Relapses when the patient was in apparent good health were ascribed to multiplication of amœbæ still viable and embedded in the tissues. The emetine when given by mouth was absorbed before reaching the intestine and consequently exerted its action from within the tissues. Attempts to administer it by enema caused irritation and diarrhœa even in non-dysenteric persons.

Further experiments led to the discovery and enunciation of certain corollaries to the foregoing. Dobell had shown that emetine is highly lethal to amœbæ in culture, acting in a dilution of even 1 in 5,000,000, but, working with H. H. Dale, he found that emetine had practically no action on amœbæ isolated from infected cats. Also methyl psychotrine, a natural alkaloid of ipecacuanha, was even more toxic for *E. histolytica in vitro* than emetine, but less toxic for animals, nevertheless when tried clinically even in large doses it had no therapeutic action. It would seem, therefore, that the therapeutic efficacy of emetine depends in some way on its action on the host rather than on the parasite directly.

Emetine and bismuth iodide, E.B.I., was introduced with the idea that it would pass through the stomach and the emetine would not be liberated until the intestine was reached. It was intended for chronic relapsing cases. It has, perhaps, lost some of its reputation because certain chronic and relapsing cases resist all forms of treatment and also because, as we have seen, the mode of action of the emetine is probably *viâ* the tissues and the giving of a preparation which will not be absorbed but reach the intestine intact is contrary to what the experiments of Dale and Dobell had indicated.

Emetine periodide, E.P.I., a Martindale preparation, was introduced because, not being acted upon in the stomach, it was found to cause less nausea and vomiting than E.B.I.

During the past twenty to twenty-five years several other drugs, mainly synthetic, have been introduced for the treatment of amœbic dysentery, and in particular chronic and relapsing cases. The chief of these are : Stovarsol (oxyaminophenylarsenic acid) introduced by E. Marchoux of the Paris Pasteur Institute, in 1923, and found good in persistent cyst-passers ; Yatren, a Bayer product (iodine oxyquinoline sulphonic acid), introduced also in 1923 as an adjunct to emetine and E.B.I., it is taken by mouth or given as enemata in 5 per cent. solution ; others which may be mentioned are Treparsol (1925), Acetarsol (stovarsol sodium, 1928), Carbarsone, an Eli Lilly preparation (*p*-carbaminophenylarsonic acid), said to be less toxic but a more powerful amœbicide than acetarsol ; and more recently Rivanol (ethoxydiaminoacridine lactate) which has some antispasmodic and antiseptic action but in amœbic dysentery has proved disappointing. Lastly, Conessine (1927), an alkaloid from *Holarrhena antidysenterica*, Conessi bark, Telicherry bark, or kurchi. The whole bark, which is an old Indian remedy, is probably better than the alkaloid prepared from it.

CHAPTER XVIII

ANKYLOSTOMIASIS

Ankylostomiasis is almost the only helminthic infestation of man in the tropics which can be said to have a history, at all events a history of sufficient interest to call for any detail.

Others have incidental points of interest, such as Manson's tidy habits leading to the elucidation of Paragonimus as the cause of hæmoptysis when a Chinese patient so far forgot his good manners as to expectorate on the floor of the consulting-room. *Wuchereria bancrofti*, the cause of filariasis, is of interest, but has little in the way of history worth recording beyond what is stated in the life of Sir Patrick Manson ; guinea-worm infestation, Dracontiasis was known to the natives of Africa many years ago, but there is little of importance to record in the history of this condition. Our remarks are, therefore, limited to ankylostomiasis.

Ankylostomiasis is a disease which probably existed in ancient days ; there is evidence—a papyrus of 1550 B.C. refers to some such condition—that it was known to the Egyptians of old, though the worm itself was not discovered until A.D. 1838. Hippocrates in 440 B.C. spoke of people exhibiting a yellowish colour (not jaundice, probably the pallor of anæmia) and suffering from intestinal disturbance and indulging in the habit of geophagy— eating dirt. In 50 B.C. the pallor of those working in mines was noted by Lucretius, and just a century later Lucan also spoke of it, but ascribed it to exhalations given off from gold and affecting the greedy delvers of it. The ' round worms ' of Avicenna appear, judging by the symptoms which he attributes to them, to have been hookworms rather than Ascaris or Enterobius. Many, indeed, hold that Avicenna (Ibn Sina, A.D. 980–1037) is the earliest to record true hookworm and ankylostomiasis. We may mention here incidentally that he also writes of the guinea-worm.

From 1611 onwards Piso in Brazil described attacks of disease characterized by intestinal disturbance, debility, anæmia and dropsy, and from 1663 onward Père Labat tells of a similar association of symptoms in Guadeloupe, and between 1745 and 1800

Bryan Edwards records the same in Jamaica. It is possible that cases of anæmia and debility from chronic malaria and dropsy from dietetic deficiency were confused with some of these. It is certain that, later, Hensinger of South Carolina confused ankylostomiasis with malaria and, in fact, called it " malarial chlorosis " ; others have made the same mistake, and indeed it was quite excusable in places where malaria was also common and at a time when nothing was known of the life-history of the parasite.

It was not until after 1838 that the worm itself began to be looked for systematically. In that year Angelo Dubini of Italy found it present in the intestine of a woman dying from pneumonia in Milan. Finding it again four years later he started systematic examination of bodies subjected to autopsy and found it in 20 per cent. and the following year (1843) he published an account of his investigations and named the worm *Agchylostoma duodenale* ; the generic name was not only pedantic but erroneous, for he derived it from ἀγκύλος, itself coming from ἄγκος (with a κ not a χ), Latin uncus or ancus = a hook or barb, because of its hook-like teeth. In the earlier cases examined by him death had been caused by or associated with other conditions—the first, as stated above, was a woman dying from pneumonia—and consequently he did not ascribe any serious mischief to their presence, just as at the present day we distinguish the person harbouring hookworms but showing no symptoms from the condition of ankylostomiasis or disease due to their presence.

Two years later, in 1845, von Siebold classified the worms as belonging to the Strongylidæ, and a clinical step in advance was made when some time afterwards Castiglioni noted their presence in dropsical and debilitated subjects ; he did not, however, connect the two as cause and effect. In 1846 Pruner found the worm in Egypt—or, perhaps, we ought to say, re-discovered it—in association with cases of Egyptian chlorosis, and in 1853 Bilharz, a name more generally associated with urinary schistosomiasis, connected the two—the worm and the ' chlorosis '—as cause and effect. The following year this ætiological connection was strongly emphasized by Griesinger, but little, in fact no, heed was paid to these findings in Egypt for another twenty years.

The next information we get comes from the Western hemisphere. In 1866 Wucherer—whose name is given to what used to be known as *Filaria sanguinis hominis*, later *Filaria bancrofti* —in Brazil found the hookworms in bodies of persons who had died from ' tropical anæmia,' and his findings were soon confirmed by other physicians in Brazil. We see, therefore, that fifteen

years elapsed after Dubini's discovery before the presence of the worm and the symptoms of anæmia and dropsy were causally connected in Egypt, and almost double that time before it was accepted in the West. For the ensuing decade post-mortem findings were noted and not till 1878 did Grassi and the brothers Ernesto and Corrado Parona show that the existence of these worms in the intestine could be determined and confirmed by observing their ova in the fæces. The next step, an obvious corollary of this, was the routine examination of fæces in all cases of anæmia, and the result was that an ever-increasing number of persons was found to be harbouring the worm.

The year 1880 is important in the history of ankylostomiasis. In the construction of the St. Gothard tunnel Italians were chiefly employed and among them occurred an outbreak of severe anæmia. The Swiss Government were asked by the Italian Government for official information. Italian physicians, in spite of the fact that hundreds of employees were found to be infested, inclined to ascribe the anæmia to bad hygienic conditions—to bad ventilation and general insanitation—in short to a combination of causes and not to one—bad conservancy—in particular. Edoardo Perroncito, Professor of Pathology at the University of Turin Veterinary School, was almost alone in maintaining that the anæmia was due to the parasite. He was convinced of this by noting at the first autopsy performed on these victims by Coloniatti, at which he was present, that 1500 worms were found in the body. Perroncito gradually bore down scepticism and opposition by showing that the anæmia could be cured by measures which would bring about expulsion of the worms. In brief, Perroncito demonstrated that, in that locality at least, " Miners' anæmia " was due to hookworms. The French physicians were the last to be convinced, but by 1895 the mine-physicians, Manouvriez and Babre, were converted.

The St. Gothard tunnel was completed in 1882, the employees were scattered and sought work in mines elsewhere—the sulphur mines of Sicily, the gold and silver mines of Hungary, the lead mines of Spain, coal mines in various parts of the Continent of Europe—Germany, Holland, Belgium, France—and in the tin mines of England. Wherever the men went anæmia was a prevalent condition.

Introduction of the hookworm into America was, we are convinced, due to imported slaves, because in the first place nothing in the early writings on the country and its diseases indicates

any such disease. Secondly, its late effects were noticed in the slaves and were designated *cachexia africana* ; other names, such as *mal d'estomac* and dirt-eating, were given to a condition for long regarded as peculiar to slaves. Thirdly—the significance of this will be more appreciated later—*Necator americanus*, the hookworm prevailing in America, is found throughout tropical Africa, even in the pygmies, and also in the chimpanzee.

At the beginning of the eighteenth century English and French observers were taking note of a disease which prevailed among the negroes of the West Indies and of Guiana. They remarked that the symptoms seemed to be assignable to one or other of two groups : (1) Alimentary disturbance, such as anorexia or ravenous hunger, depraved taste, constipation alternating with diarrhœa. (2) Anæmia and circulatory disturbance, with palpitation, dyspnœa, soft rapid or irregular pulse, cold and pallid skin, pale mucosæ, weakness even to exhaustion, and wasting with dropsy, not infrequently ending fatally. On account of these symptoms the disease had several synonyms, among them *mal d'estomac*, *mal de cœur*, dirt-eating, geophagy, *anæmia tropicalis*, *cachexia africana*, *cachexia aqueuse*, *oppilação* (constipation).

In the early years of last century, in 1808, Joseph Pitt had remarked that dirt-eating and anæmia were common among the poor whites and the lower class negroes in the Southern American States. The mortality due to it was by no means inconsiderable and it soon increased till it caused grave concern. This condition of anæmia, pallor and debility was accounted for as the result of the practice of eating earth—by some regarded as a dirty habit, by others as deliberate for purposes of suicide. In Europe, Treviso described it in children under the name *allotriofagia*, *mangiare sostanze non alimentari*. These authorities were transposing effect and cause ; pica occurs in conditions other than hookworm infestation.

In 1820 James Thompson gave a good account of the disease and its ravages among slaves in Jamaica and Bryan Edwards went farther and recorded that, in his opinion, *mal d'estomac* (*i.e.* ankylostomiasis) and *trismus nascentium* (*i.e.* tetanus neonatorum) were the two chief causes of death among the negroes there.

Not, however, till 1893 was the first case of ankylostomiasis recognized, by W. L. Blickhahn, in America (*Medical News of Philadelphia*), the patient being a brick-maker from Westphalia, and almost certainly an imported case. The next was recorded from Texas in 1894 by Frank Herff, and thereafter reports began to come in from all over the country.

Those interested in parasitology, on examining the worms, noted that in many cases, in fact in most, the hookworm present differed in several points from that which had been described in worms found in Europe. Lutz of Brazil had noted the fact earlier, in 1888, but it was not until 1902 that Dr. C. Wardell Stiles, of the United States Bureau of Animal Industry, and a famous zoologist, described this, as it was thought, new species and named it *Necator americanus* or *Uncinaria americana*. The anæmia recognized to be common in the Southern States had been thought to be malarial in origin, but investigation now showed that some of the cases at least were due to hookworm infestation. Yet more ; Italian and other workmen from Europe had gone over to Brazil to work for part of the year on the coffee plantations ; they became infested there with the Necator and on return to their own country carried the new infection with them. Here we find an explanation of the fact that, in the mine-workers on the Continent the prevailing hookworm is *Ancylostoma duodenale*, whereas outside the mines most of the infection present is due to *N. americanus*. This latter name is misleading because, as already mentioned, there are strong reasons for believing that the parasite was brought over by the slaves from Africa. Apart from Africa the same species has been found in India, Ceylon, Fiji and the Philippines.

Below is a list of the more important of the earlier recorders of hookworm infestation in the different countries. Such has some historic interest and it seems a pity that the record should be lost, as it almost certainly will be in the course of time.

West Indies :
  1. Jamaica. Hunter 1796, Telford 1822, Gregory 1831, Mason 1833, Ferguson 1836.
  2. Dominica. Imray 1843.
  3. St. Lucia. Levacher 1840. -
  4. Grenada. Chisholm 1799.
  5. Trinidad. McCabe 1818.
  6. St. Thomas. Dons 1833.
  7. St. Martin. Grall 1835.
  8. Porto Rico. De Cordoba 1831.
  9. Guadeloupe. Moreau de Jonnées 1816, Duchaissaing 1850.
  10. Martinique. Savarésy 1809, Noverre 1833, Rufz 1869, Carpentin 1873.
  11. San Domingo. Chevalier 1752, Desportes 1770.
Guiana :
  British. Rodschied 1796, Hancock 1831.
  French (Cayenne). Bajon 1780, Segond 1833.
  Dutch (Surinam). Cragin 1836, Hille 1845, Landré 1852, v. Leent 1867.

Brazil :
Jobim 1835, Sigaud 1844, Rendu 1848, St. Hilaire 1849, Wucherer 1866, de Rocha 1868, Vauvray 1869, de Moura 1872, Souza-Vaz 1878.
Bolivia :
Galt 1872.
Southern United States :
Louisiana. Chabert 1820, Duncan 1849.
Alabama and Georgia. Lyell 1849.
South Carolina. Hensinger 1852.
West Africa :
Senegambia. Moulin 1866, Thaly 1867, Borius 1882.
Guinea Coast. Clarke 1860.
East Africa :
Comoro group. Monestier 1867, Grenet 1867.
Zanzibar coast. Lostalot-Bachoué 1876.
Egypt :
Pruner 1846, Bilharz 1853, Griesinger 1854.
Europe has already been mentioned (p. 842).

The year 1898 is an important one in the history of ankylostomiasis. Till then infection was believed to occur *per os* only, through eating with unwashen hands, by swallowing infected dust, by association with horses or other domestic animals. Incidentally, horse-haulage was discontinued in Hungarian mines on this belief. It was not known that the hookworm infesting domestic animals not only differed from those attacking man, but did not as a rule infest man. The dog hookworm, *A. ceylanicum*, is an exception, having been found in a small number of East Indians by Clayton Lane in 1913. This species was first described by Looss in a civet cat from Colombo ; Lane found it commonly in dogs and cats in Bengal. The fact that domestic animals harbour it introduces a difficulty in prophylaxis. Leuckart had shown in 1866 that oral infection occurred and twenty-one years later Lichtenstein confirmed this experimentally. But in 1898 Arthur Looss, Professor of Parasitology in Cairo, accidentally let a drop of hookworm culture, that is a fluid containing ancylostome larvæ, fall on his hand. He was too busy at the moment to trouble about it and all he noticed was a certain degree of local irritation as the drop dried. Thinking over this afterwards he put his suspicions to the test by examining his fæces at intervals for hookworm ova and in due time found them. He concluded, therefore, that he had been infected by the drop of culture which fell on his hand. He confirmed this by subsequent experiment. For a time he was subjected to much hostile criticism but gradually he gained the profession over to his view and showed the course of development and passage in the body from the time of penetration of the larvæ

into the skin—preferably the thin skin around the ankles, where they are responsible for the ' ground itch ' or ' dew itch ' and pani-ghao, the local name in Assam, which has the same significance, familiar to natives working bare-foot in hookworm countries— thence by the lymph channels or the blood capillaries, to the veins and so to the lungs. From there they passed to the bronchioles, bronchi, travelling up the trachea to the larynx and pharynx, then *viâ* the œsophagus to the intestine where they grow to maturity, suck blood and possibly produce a toxin which causes anæmia, œdema, fever—in short, the symptoms of ankylostomiasis.

This was a discovery of no mere academic importance, for it explained why previous methods of control had proved ineffectual and indicated new methods likely to be more effective, namely avoidance of contact between the larva-bearing soil, mud and water, and the bare skin—in other words to go about barefoot was to court infestation.

Looss's epochal monograph was published in 1911 ; in this all that was known and much that was till then unknown were summarized. It is from this that we may trace all the preventive work that has been undertaken in the tropics and subtropics where the hookworm throve and worked great havoc until proper measures based on these lines were effected.

As already noted hookworms in different parts of the world belonged to one or more species which were not mixed. Later visitors from one might bring their species with them to a place where a different species occurred in nature and so lead to a mingling of them in the new locality. Thus, in Fiji the indigenous native was attacked by Necator only, but in urban areas where the Fijian associates with the Indian coolie Ancylostoma is also found, and *vice versa.* Again, among the Malayans nearly all the hookworms (98·9 per cent.) are Necator, whereas in Chinese coolies from 35 to 85 per cent. harbour Ancylostoma. Chinese born in Malaya often adopt the Malayan customs and modes of living and in them the proportion of Ancylostoma decreases and that of Necator rises.

Generally speaking, as Samuel Darling pointed out in 1920, *A. duodenale* is distributed between 35° and 20° N. latitude. It is found in the Cornish mines, in the Mediterranean countries, in Northern Africa and in Egypt. Coolies from India and Java introduced it into America and the Antilles ; Brazil and other parts of South, Central, and North America became infected by immigrants from the Mediterranean and the Levant and by the Japanese and Chinese. As mentioned above, Indian coolies

introduced it into Fiji, and the Chinese, Japanese and Portuguese brought it to Polynesia, the Philippines and Australia.

Necator americanus occurs naturally south of 20° N. latitude in Eurasia, Africa, Indonesia and Polynesia. It was brought over to America originally by the slaves and later by East Indian coolies from British India and Java and has since spread from Virginia to the Argentine. In the Southern States Necator alone was found, because this was the species introduced by slaves from Mozambique. Among the kaffirs of South Africa, among the Solomon Islanders and Polynesians the same is noted—Necator only is present.

The parasite has had several names. Dujardin called it Dochmius, Cobbold named it Sclerostoma, Dubini Agchylostoma, later Anchylostoma or Anchylostomum (both etymologically wrong) and now Ancylostoma, and the southern genus Necator (slayer) or Uncinaria (uncus, ancus = a hook) by Stiles. *Duodenale*, the specific name of the former is not quite justifiable except by the laws of nomenclature, for it inhabits the upper part of the jejunum rather than the duodenum. *Americanus* as the specific name of the latter is too narrow in its range.

In some parts of the world the rate of infestation is high, though less now than formerly, since a knowledge of the life-history of the parasite has enabled preventive and control measures to be taken up on scientific lines. Thus, in 1904 Bidder found that in some Continental mines 80 per cent. of the men were infested ; Clayton Lane the same year reported 70 per cent. incidence among the prisoners in Puri and Chupra gaols and he quoted the following figures. Andamans 76, Durbhanga 83, Dacca 12 per cent., and Bentley in Assam found only one free among 600 examined. In 1911 Endicott and Gunn writing in America found hookworm very prevalent in the deep mines and believed that the parasites were being still imported from Cornwall, Austria, Italy and elsewhere. Fifty per cent. of the immigrants from Porto Rico they found positive, of the Hindus 63 per cent., of Japanese 56, of Chinese males 39, and Chinese females 20 per cent.

From more recent returns we find that this high incidence has been much reduced all over the world. The latest figures (1936) show that in the United States hookworm infestation is limited to mining areas in only six States and to certain rural areas of the South. In France the diminution since the 1904–07 inquiry has been very marked, and it is now confined to certain mines in the Loire area. In Hungary only three mines were affected out of

thirty-three ; in Spain one mine and one rural area in Murcia. In Tunis the mining population appeared to be free, but in four cases among the native population infestation was found to be heavy.   In short, the disease is no longer serious in Europe, for those living under hygienic conditions ; most mines are either free altogether or but lightly infested.

Passing to the history of treatment and control we will deal first with preventive measures, although the use of curative drugs preceded prophylaxis and the investigation to find the ideal is still proceeding.

We have told how the completion of the St. Gothard tunnel led to dispersion of infested miners over Europe and spread of ankylostomiasis on the Continent. By 1903 so serious had the results become that Germany started a campaign to deal with it. Those infested received drug treatment, new men applying for work were examined and if found infested were excluded from employment underground until free ; sanitary conveniences were installed. The result was that, whereas in 1903 the infestation rate was 13·1 per cent., by 1914 it was only 0·17 per cent., or one-seventy-seventh of the former prevalence.   In Belgium, as in more recent times, the methods of Germany did not find ready acceptance ; precept was preferred to practice. Co-operative efforts were undertaken to educate the employees, more than one-third of whom were illiterate, and those infested received treatment ; although latrine accommodation was not installed, at all events adequately, nevertheless in Liége where the disease was severe the incidence fell from 22·8 per cent. in 1902 to 1·2 per cent., or nearly one-twentieth in 1913.   In Holland a more prophylactic régime was instituted, milder, and, compared with the " curative, drastic and expensive " campaigns of Germany and Belgium, inexpensive. The infestation rate was reduced from 25·1 per cent in 1904 to 0·3 per cent. in 1913, less than one-eightieth. The incidence was worst in the Sicilian sulphur mines. In 1898 50 per cent. of the miners were found infested, but nothing was done. By 1912 the prevalence was even greater and treatment was started in two mines with some success. In a centre on the mainland in the Romagna disinfection and treatment proved very successful and a report stated that the incidence which in 1908 was 38·2 per cent. had been reduced by 1914 to 0·3 per cent. or $\frac{1}{127}$.

Austrian and English mines being drier than those of Germany, Belgium and Sicily were less favourable to development of the

parasite. In the tin mines of Cornwall and Devon examination of employees and general sanitary measures were introduced with good effect ; no extensive prophylactic undertakings were needed. In Spain the mañana principle held as usual and little was done. In the nineteen-twenties in the lead mines of Linares the infestation rate ranged from 50 to 90 per cent.

Though introduced by workers in trades other than mining, e.g. brick-makers in Holland, Germany, Italy, the Balkan States and Southern Russia, and also among those working in the rice-fields and on the land, ankylostomiasis does not progress among them to any extent, for the climate, in the north at least, is too cold for ready propagation of the parasite, nor do the employees work barefooted. Abroad, in tropical and subtropical countries, however, matters are very different. Natives work barefoot, are sanitarily heedless, will not use latrines even when provided except under compulsion, but defæcate on the ground round their dwellings and, infested, will keep the soil continually re-infected, while irrigation of plantations helps to keep the ground moist and to favour development of the parasite.

Ashford of Porto Rico and W. W. King, the latter an officer of the United States Public Health and Marine Hospital Service, came to the conclusion at the beginning of the present century that practically one-third of the deaths in Porto Rico were due to hookworm infestation and the anæmia resulting therefrom. In 1904, therefore, a Commission was appointed to carry out an anti-hookworm campaign there. Subsequently, campaigns were undertaken in the United States by various State Boards of Health and in 1909 by the Rockefeller Sanitary Commission whose work, as that of the Rockefeller Foundation established in 1913, was two years later merged into that of the International Health Board. Since that date one of the chief activities of the Board has been the prophylaxis and treatment of hookworm infestation. The programme was similar in all : A sanitary and infestation survey followed by an intensive campaign of cure and prevention. At first the press was in many places hostile, then indifferent, and finally warm supporters—they came to scoff and stayed to pray. At the same time medical schools gave, as part of the curriculum, instruction in the diagnosis and treatment of intestinal parasitism.

Propaganda work comprised the exhibition of posters, lectures and demonstrations to children in the schools and talks with parents and adults when visits of inspection were carried out. Field work included travelling dispensaries and later house to house canvass. The customary method is first to map out the district,

and next to take a census of the population, numbering or otherwise noting the houses. The fæces of all are then examined by trained microscopists and any person found infested receives treatment. At the same time (or more often as a preliminary) latrines are installed and educative measures instituted. As there is the proverbial difference between taking a horse to water and prevailing upon him to drink, so there is often among the natives a considerable hiatus between installation of latrines and the habitual use of them.

From 1913 the International Health Board co-operated, when invited, to undertake campaigns in British Colonies—British Guiana, Antigua, Trinidad, St. Lucia, Grenada—also in Egypt, in Panama, Nicaragua, Costa Rica, Salvador and Guatemala. By 1915 the anti-hookworm undertakings of the Board had extended to ten southern States and thirteen ' foreign ' countries (i.e. foreign to America) ; the Great War led to some retardation, but by 1921 the work was going forward in forty-one States and countries—Jamaica, Porto Rico, Brazil, Colombia, Dutch Guiana, Australia, Papua, British North Borneo, Ceylon, India and Siam, in addition to those already named. Some 4,000,000 persons had been examined and more than half of these had been found infested and received treatment.

Soil contamination is a very serious problem in hookworm countries. W. E. Cort and G. C. Payne in 1922 showed that the larvæ might persist in soil for six weeks, according to the nature of the soil, and J. B. McVail demonstrated, the same year, that larvæ will pass through septic tanks and emerge alive, even when such tanks are properly worked, and in greater numbers when they are overworked ; also that chlorination which is adequate to destroy Bacterium coli has no effect on hookworm larvæ. Looss had previously shown that the larvæ could live for three months in water and could even survive after being frozen.

The benefits of the Rockefeller efforts were by no means limited to the disease treated, for a great impulse was given to sanitation in general, by prevention of soil pollution, while the scientific investigation of parasitism, especially intestinal parasitism, was much advanced.

In conclusion, a few words are called for on the history of remedial, therapeutic treatment, apart from prophylaxis or as a part of prophylaxis, in so far as treatment of the infested reduced the source and thereby the amount of possible infection.

From the early days when the presence of the hookworm was discovered and was suspected of being the cause of anæmia and

disease the then known anthelmintics were tried but without success. In 1879 Bozzolo had, in addition, made trial of thymol —a phenol with the formula $C_6H_3(CH_3)(OH)C_3H_7$, obtained from the oils of *Thymus vulgaris* and other plants, and a drug which later attained a high repute—for hookworm infestation among brick-makers in northern Italy and in 1880 he and Pagliani reported concerning workmen employed in the St. Gothard tunnel that no way of killing or expelling the worm was known. At the same time Perroncito had noted by experiment that immature hookworm larvæ died immediately when subjected to thymol solution of a strength of 0·5 per cent., and that mature larvæ would not survive such exposure for longer than 8–10 minutes. Also that ethereal extract of male fern killed them in even less time. Bozzolo, and not he alone, was sceptical of these findings, or at least of their application to patients and laid more stress on measures of prevention.

In 1881 Bozzolo again tried *Filix mas*, but finding that many of those infested would not tolerate this he turned again to thymol, giving doses larger than he had given previously, and announced that by this means he had cured six patients. Lutz in Brazil made trial of it in 1883 and reported that in his hands it had proved more effective than male fern. Thymol thereafter came more and more into favour, but cases of intolerance were recorded, gastro-intestinal disturbance being caused and toxic symptoms such as tinnitus, deafness, dyspnœa with slowing of the respiration rate, rise followed by fall of the pulse rate, lowering of temperature and collapse. These symptoms were the result of absorption and solvents of the drug had, therefore, to be avoided, such as alcohol in particular, and unless the native is kept under observation he will, despite orders, take a drink of alcohol to obviate the taste or disagreeableness of the drug.

In consequence, for the past fifty years many remedies have been suggested and attempts made to find the ideal drug ; one whose therapeutic dose was low as compared with the toxic, and yet would be easily dispensed, readily taken, effectual, and yet give rise to as few and as mild by-effects as possible.

Thymol maintained its place till 1917, although others had been brought forward, notably β-naphthol ($C_{10}H_7OH$), chloroform and eucalyptus. These last were suggested and had been tried in 1906 for cases in which thymol had proved ineffectual. Then oil of chenopodium—*Chenopodium ambrosioides* var. *anthelminticum*, American wormseed, Goose-foot, Jerusalem oak—which had been recommended as long before as 1900 by Schüffner and Vervoort in

Sumatra, displaced thymol because its maximum safe dose was more potent than thymol, it was less expensive, more easily administered and less unpleasant to take. Experience, however, showed that its constituent active principle was not constant, different preparations varied considerably in strength and hence in toxicity and standardization was undertaken to obtain a product which should contain a constant amount of the active principle, *Ascaridole*, $C_{10}H_{16}O_2$. R. L. Levy, using it in America, reported that it was good not only for hookworm but also for whipworm (Trichuris) and tapeworm, and V. G. Heiser, as early as 1915, recorded its use in " over ten thousand cases with success and no danger."

We may mention here in passing that during the same period advances in diagnostic technique were being made ; direct examination of fæcal smears gave way to centrifugal and other methods of concentration, as for example by emulsifying in saline of fixed specific gravity, by which the ova might either be thrown down in the sediment or float to the top of the fluid. Of these methods those of Willis, Stoll and Clayton Lane should be particularly noted.

That oil of chenopodium did not fulfil all expectations is evidenced by the fact that from 1921 onwards it began to give way to a new preparation, Carbon tetrachloride, CCl_4, the advantages claimed for this being that it was cheaper than oil of chenopodium, was effective for ascariasis as well as for ankylostomiasis, that it was not depressing and needed no after-purge. It was introduced by M. C. Hall and used first on dogs. On further investigation carbon tetrachloride was found to act more effectually on Necator than on Ancylostoma, whereas oil of chenopodium, or its active principle, ascaridole, had greater action on the latter, Ancylostoma. Hence, when both infestations were present, as is common in the West Indies, the best results are obtained from a combination of the two, the dosage being 2 c.c., composed of four parts of the tetrachloride to one of ascaridole.

Further efforts to find the ideal drug resulted first in Trichlorethylene, $CHCl_3 : CCl_2$, and next in 1925 Hall and Shillinger introduced Tetrachlorethylene or bichloride of carbon C_2Cl_4, which they found as effective as carbon tetrachloride and as safe while being more pleasant to take ; its cost, however, was two or three times as great. Another drug suggested and tried was Hexylresorcinol with the formula $CH_3(CH_2)_5C_6H_2(OH)_2$. A solution of this in olive oil went under the name *caprokol.*

One other method of treatment may be mentioned as of transient

historic interest ; it never gained in popularity and the reason is not far to seek. This was the de Rivas treatment, reported by him in 1927 as the " intraintestinal thermal method " which consisted in administering directly by tube into the duodenum or *per rectum* 500–1000 c.c. of salt solution run in slowly at a temperature of 45–47° C. Since the favourite habitat of the hookworm is the upper part of the jejunum, if given by the lower route the fluid would have a long way to travel even after it had negotiated the ileo-cæcal valve.

CHAPTER XIX

TROPICAL DISEASES CONNECTED WITH FOOD

In a work concerned with the history of disease in the tropics certain conditions associated with diet and dietetic deficiencies, avitaminoses and food-poisonings come up for consideration—conditions which are, so to speak, tropical diseases by chance. We mean by this that, were the articles of food—some of which, it must be remembered are used all the world over—to be used to the same extent or in the same way·in temperate climates the range of the disease would be correspondingly extended.

The scope is not altogether easy to define. Beriberi and epidemic dropsy, for instance, will be regarded for our purpose as diseases of warm climates ; pellagra and pellagroid conditions are known to occur in temperate as well as torrid zones, but are of the nature of clinical rarities in the former, though of everyday occurrence in the experience of those practising in the tropics. Again, certain toxic fruits and plants are found growing in the tropics and subtropics and are used as food by the natives, such, for example, as bitter cassava (manioc) and akee (*Blighia sapida*) ; others are eaten and cause sickness and death through inadvertence or are employed for homicidal or criminal purposes, such as stramonium, *Gloriosa superba*, *Illicium religiosum*, *Hippomane mancinella* (Manchineel apple) ; others as drugs indulged in by addicts, opium, Indian hemp (*Cannabis indica*), and so forth.

We see that these many conditions may be roughly divided into two groups : Avitaminoses and Food poisons. Under the former we shall give an account of beriberi and scurvy ; under the latter of Akee or poisoning by *B. sapida* and Jake paralysis or Jamaica Ginger poisoning. Belonging to neither group solely, but partaking of the nature of both, so far as present knowledge goes, are epidemic dropsy and pellagra and pellagroid conditions which, according to some authorities, are avitaminoses, according to others toxic in origin, or a combination of both. Under this head mention will be made of pellagra itself, of kwashiorkor, of

A and B avitaminosis of Nigeria, and of the so-called ' central neuritis ' of Jamaica.

The various poisons, some of which have been enumerated above, will not be dealt with, chiefly because in spite of their clinical importance they have no interest for the medical historian, and in the second place because their characters, the symptoms they produce and so on, are already treated fully enough in works on toxicology.

Among avitaminoses we shall add but little to what has been already said regarding scurvy, interesting and historically important though it is, for, although it was a veritable scourge in the Navy and the wrecker of expeditions in the eighteenth and nineteenth centuries, and many of these involved service in the tropics, it cannot be regarded as a disease of those regions, being, in fact, more common in non-tropical lands, and even in the Arctic.

I. AVITAMINOSES

By way of preliminary we would like to sound a note of warning. There has, of late years more particularly, been a tendency to ascribe certain obscure forms of disease in the tropics to dietetic errors and food deficiency with little, in some instances with no, attempt to furnish scientific proof therefor ; the grounds for such statements often are mere plausible hypotheses. To name but one, tropical ulcer. After bacteriological and protozoological investigation fails to reveal any constant association of organisms and when such organisms as are found are isolated and cultivated but do not on experimental inoculation produce similar lesions in animals, it is all too easy to fall back on a malnutrition theory and to say that if the race as a whole were better nourished they would not so suffer, and to rest content with this.

It will be acknowledged freely by all who have practised in the tropics that among native races the problem of nutrition is one of greater importance than in our own ; at the same time much vague inference and many hasty conclusions based on in-adequate observation have been allowed to replace scientifically planned experiment—a fact the more deplorable in that the opportunities for research are not lacking.

The days have long gone by when we were taught that a complete and adequate diet consisted of a certain amount of proteins, fats, carbohydrates and salts in their proper relative proportions, together making up so many calories according to the nature of the work to be performed. It has remained for

research in the present century to show that even with sufficient calories growth is not promoted nor life supported indefinitely if certain food essentials (later known as Vitamines, then Vitamins) were wanting.

Most of these deficiency diseases, or to use a more modern term avitaminoses, are diseases of civilization. The native in his wilder state, living on the natural fruits of the earth, does not suffer from avitaminoses ; he may perish from starvation when his crops fail with consequent widespread famine, but he does not on that account suffer from ' deficiency disease,' but when civilization introduces polished rice, white flour, tinned meat and vegetables, then we see the symptoms of vitamin lack.

That faulty diet might cause disease is no recent development of knowledge ; it can be traced back at least 400 years. As long ago as 1502 João de Barros described in the following words the scurvy which afflicted crews of vessels lying off the East African coast :

Many were stricken, whereof some died. . . . Their gums were so swollen that their mouths could scarce contain them, and they rotted till they cracked and burst, as if the flesh were dead : a thing most pitiful to see. And this affliction we afterwards found to be due to the consumption of meat, salt fish, and ship's biscuit, corrupted by overlong keeping.

Again, João dos Santos, a Dominican missionary who visited East Africa in 1586 and, some twenty years later (1609), recorded his travelling experiences in Mozambique, gave an unmistakable account of nyctalopia and spoke of it as being possibly due to the food and attacking the Portuguese and natives equally. We may mention here that night-blindness was a condition recognized in China ages ago and moreover regarded as of dietetic origin. Chinese medical literature of 1500 B.C. refers to it and even suggested liver therapy. It is but right, however, to say that many other remedies were also recommended for the condition, some of them of but little biological activity, such as bile, brains, blood and honey. Flying-fox dung was a popular remedy and tortoise shell was thought to be almost as efficacious as sheep's liver ; also popular, but not looked upon as so efficacious as some of the above, were bat and sparrow excreta.

After the writings of Lind and the reports of Captain Cook's voyages on the prevention of scurvy we, at the present day, cannot help a feeling of surprise that the idea of ' food deficiency '

did not take rapid hold. We must, however, bear in mind that notions on diet and nutrition were of the vaguest in those days, that *positive* causes were expected for all morbid conditions. Less than half a century ago bacteria or their toxins, protozoa, and helminths were assiduously looked for in the causation of disease, as we have seen in the cases of malaria, yellow fever and shall see in beriberi, epidemic dropsy, and others, and it would seem paradoxical—some maintain a similar attitude to-day—that the *absence* of a thing could cause disease, or, as it has been aptly put " it was difficult to conceive a causation prefixed by a *minus* sign."

To dwell in any detail on Vitamins and Vitamin Research would be beyond the scope of this work, but in view of its importance in beriberi, pellagroid conditions and others of particular interest to tropical workers a brief sketch, a bird's-eye view, as it were, will not be amiss.

In 1881, Lunin at the Bunge School at Basel analysed milk and tried the experiment of feeding mice on an artificially prepared ' synthetic milk.' The animals did not thrive and Lunin came to the conclusion that milk, natural raw milk, must contain unknown ingredients without which life could not be supported. His remarks met the usual fate accorded to the ' wild notions ' of scientific innovators—nobody paid any attention. A decade later Socin was led to the same conclusion and then followed an even longer interval, till 1905 when Professor Pekelharing wrote : " There is a still unknown substance in milk of paramount importance in nutrition. Without it, assimilation fails, appetite is lost and in the midst of apparent plenty animals die of want." Pekelharing had previously been studying the problem of beriberi in Java, but in this his acumen was blunted and he concluded, in 1887, that the disease was due to an organism present in the blood of patients (see later, p. 877). The work of Christiaan Eijkman, the first Director of the laboratory at Batavia for studying beriberi, is recorded in the sequel, and we owe much to G. Grijns, another Dutchman, who in 1901 gave a more substantial form to the idea of a deficiency, or negative cause, the " absence of something essential to nutrition " being capable of setting up disease. Six years later W. L. Braddon confirmed the observations of Eijkman relative to rice and the effects of feeding birds with polished rice and close on this came the eloquent researches and experimental work of H. Fraser and A. T. Stanton (later Sir Thomas Stanton, K.C.M.G., Chief Medical Adviser to the Secretary of State for the Colonies) which is given in detail in the section dealing with beriberi.

In 1911 Casimir Funk, stimulated by the work of Grijns, Fraser and Stanton, carried out investigations at the Lister Institute and succeeded in isolating from rice-polishings an extract which was preventative and curative of beriberi. It is to Funk that we owe the term *Vitamine*, employed in his paper published in 1912 under the title *The Etiology of the Deficiency Diseases*. In this he speaks also of pellagra and scurvy, regarding the former as a ' deficiency disease '—an opinion considerably in advance of his day. The reason for the term was that he regarded the substance, whatever it was that was essential for life and growth, as an ' amine ' or ammonia substitution derivative. Later, when it was discovered that these principles were not amines, J. C. Drummond in 1920 made the happy suggestion that the word was a convenient one but that the possibly erroneous deduction that they were amines would not be perpetuated and might soon be forgotten if the terminal letter was dropped and the spelling *Vitamin* has since been generally adopted and his prediction has come true—nobody now, when speaking of vitamins, has any thought of their being amines.

Some, at least, of the vitamins are complex. Thus, R. A. Peters, the Whitley Professor of Biochemistry, University of Oxford, has shown that Vitamin B, which in the early days of beriberi research was thought to be, like the early French Republic, ' one and indivisible,' contains at least six vitamin components : Vitamin B_1, also known as aneurin or torulin, the antineuritic vitamin to whose absence beriberi is attributable ; B_2 which can be split into two, lactoflavin and the rat antidermatitis component to which has been assigned the term Vitamin B_6 ; B_3 and B_5 which include the chicken antipellagra factor ; and, finally, B_4 whose position is at present not clear, some regarding it as concerned in preventing acrodynia or ' pink disease,' though others ascribe this to deficiency in Vitamin B_2. Vitamin B therefore contains the antiberiberi factor, the human antipellagra, ' B.P.' factor, the factors preventing Black-tongue in dogs, heartblock in pigeons, and ' Bios,' and growth factors for organisms.

The above sketch must suffice here as introductory to the consideration of what is historically the most important of the avitaminoses to the tropical practitioner, namely Beriberi.

A. BERIBERI

The name ' beriberi ' is said by some to be derived from the Malay *biribi*, meaning a tripping or jerky gait, by others from the

Hindustani *bharbari*, a term used for ' swelling ' and particularly œdematous swelling. Other names by which the disease is known are *kakké* in Japan, though of Chinese origin and derived from *kiaku*, leg, and *ka* or *ki*, disease. In Cuba the name given to it is *hinchazon* (puffiness, dropsy) *de los negros*, the wet form being more obvious than the dry ; in Minas Geraes, Province of Brazil, almost the same word is used, *inchação*, which has the same significance, whereas in Matto Grosso the non-committal word *perneiras*, that is, disease of the legs, is used. The French *barbiers* is merely a corruption of beriberi.

- In spite of the terms indicating the wet or œdematous form —in India, Japan, Brazil and Cuba—from quite early days a paralytic and a dropsical form were distinguished, and a mixed form, in which dropsy came on late, was known.

Kakké, originally, as already stated, a Chinese word, occurs in a Chinese work dating about 200 B.C., and in another work of about 70 B.C. a description of the disease, though not a very clear one, has been found. Dr. Manson-Bahr speaks of a medical work, *Neiching*, attributed to Hwangti (2697 B.C.), in which there is thought to be a reference to this disease (Manson's *Tropical Diseases*, 1935, 10th edition, p. 393).

In works of Chinese writers of the third, seventh and eighth centuries A.D. several references may be found and in a work which appeared in the tenth century a distinction is drawn between the dry paralytic form and the wet dropsical kakké.

In Japanese works of the ninth century are references which can easily be fitted to descriptions of beriberi, but in these and other medical works of later date *kakké* is confused with heart disease, rheumatism and dropsy, possibly of renal origin. In more recent years confusion has arisen between beriberi and malaria cachexia on the one hand and hookworm infestation with anæmia and œdema on the other. Bontius in the seventeenth century described the condition as he saw it in the East Indies, and Tulpius, a Dutch physician, speaks of it on the Coromandel Coast ; Paxmann, Lind and Fontana mention its occurrence on the Malabar Coast and Malcolmson on the east coast of Africa.

Its occurrence in the New World seems to have been of much more recent date—at least I have not been able to find any early reference to a condition in any way resembling it, none earlier, in fact, than 1860 in Brazil and in Guiana.

Hirsch, writing twenty years later, stated that it then existed over a large part of the tropical and subtropical zones of both the eastern and the western hemispheres, but that its limits of

more intense prevalence were fairly narrow, and he gives the geographical distribution as follows :

Japan : From Nagasaki to Hakodate ; in earlier days it was confined to the trading ports, but later spread inland to Kodzuke and Oshin. In China fairly generally distributed over the parts then known ; in Burma, Singapore, the Malay Archipelago, Sumatra, Borneo, Celebes, the Moluccas, New Guinea, and Java. In India : Madras and Lower Bengal, but not Bombay ; in Ceylon, and Mauritius and Réunion, and by 1900 it had been seen in Assam and among Chinese immigrants in Australia.

The history of the disease in the Philippines is of considerable interest because we can trace it back for some 350 years and perhaps even longer. The following is a brief résumé of the main points. The first mention of the disease we have been able to trace is a statement made in 1543 when Villalobos, the Spanish Governor was in Mindanao, though it is probable, seeing that the food of the natives was the same before the coming of the·Spaniards as afterwards, that the disease existed there earlier than the middle of the sixteenth century. " The people began to get sick and to die immediately . . . after gradual swelling, especially annoying the abdominal region. For the illness which they called ber-ber no remedy could be found." Villalobos was himself a victim. Forty years later, in 1582, Ronquillo, the Governor at that time, prepared an expedition the personnel of which included 300 Spaniards and 1500 Filipinos, most of whom came from Pangasinan and Cagayan, and its object the conquest of the Moluccas. After the surrender of the island of Montil and the fortress of Tidore, beriberi broke out among the invaders and so many died that the expedition was abandoned.

Some time between 1627 and 1631, when he was physician to the Dutch East Indies Company, Jakobus Bontius took up its study scientifically. In his works on tropical medicine published posthumously in 1642 he gives an account of beriberi, detailing concisely, clearly and accurately the chief symptoms, in fact this is perhaps the first orderly description. His recommendation of shark's liver to be eaten raw with salt, as a specific remedy for a condition associated with impaired vision and at times transitory blindness among those who sailed to Amboina and the Moluccas suggests a forestalling or even intelligent anticipation of the modern view of connecting night-blindness with diet deficiency.

The next note of importance in the history of beriberi in this part of the world is an account of the symptoms given in 1768 by a Dominican friar, Fernando de Santamaria, who writes in Spanish

of which the following is a translation : " The entire body swells through excessive dampness . . the one efficacious remedy is rubbing the soles of the feet with Burgundy pitch and covering up the legs, especially at night." In what way this form of treatment would be efficacious we cannot conjecture.

Then follows another interval of more than a century. In 1882 an outbreak followed a typhoon and a cholera epidemic. The outbreak, it was argued by those most likely to know—Dr. Felipi Zamora, Dr. Koeniger, a German, and Dr. José de Antelo, the Provincial Sub-Deputy of Health—was beriberi and was ascribed to " mal- or under-nutrition, exposure to the effluvium washed up by the tide and the mercurial changes in temperature " [whatever that implied]. In that outbreak Europeans escaped. Twenty-eight years later the Americans took up the investigation and R. P. Strong made the Bilibid prison experiments which are referred to below (p. 887) ; in the interval many had written about the disease, notably Manuel Guerron, Benito Valdes and Fernando Calderón. Although we are anticipating events which will be recorded in more detail later, we may briefly sum up here the work on this disease to give sequence to the history of it in the Philippines. In 1923 a Beriberi Investigation Committee was constituted, largely at the instigation of Dr. José Albert, and the members were United States Army Medical Officers and Filipino physicians, and their terms of reference were to " study closely from all points of view the problem of beriberi, inasmuch as it is a matter which affects directly all the peoples of the Far East and of the Philippines particularly."

In 1926, in consequence of a resolution passed at the Congress of the Far Eastern Association of Tropical Medicine, held at Tokyo the year before, another Committee on Beriberi was appointed ; it dealt more with Infantile Beriberi and is referred to later (p. 891).

An outbreak which occurred among employees in St. Paul Island as recently as 1931 is worthy of record. This island is situated in the Indian Ocean about midway between the Cape of Good Hope and the Western Australian coast. In 1928 a French vessel, the *Espérance*, left Table Bay for the island to establish a lobster and crayfish canning factory. In May 1931 there came a dramatic call by wireless for help. Of the 132 employees one-fourth were suffering from beriberi. Thirty deaths occurred before the *Austral*, which was sealing in southern waters and received the call, could arrive. The victims were mostly natives from Madagascar who had persisted in disregarding orders concerning their diet and had eaten white rice instead of red.

There is no record of the presence of beriberi in the Western hemisphere until recent times. In the French West Indies it was recorded at Guadeloupe among negroes imported from the Congo in 1859 and at Cayenne, French Guiana, in 1865 among imported coolies. In the French Antilles the disease occurred mostly among the Chinese, but sometimes was observed in negroes and it went by the name *maladie de sucreries*, or ' sugar-works disease ' since it affected labourers employed in them. There is an account of a disease in Ceará in 1825 which may possibly have been beriberi and accounts of the condition in Brazil are found earlier than in other parts of the West ; thus, it was certainly present in Minas Geraes in 1858 and again in 1861, whereas the first mention of it in Cuba dates from 1873 when the negroes working on two plantations were seriously attacked and the fatality rate was reported as very high, 60–75 per cent. The presence of beriberi on ships we will speak of later.

In the introductory remarks to the present chapter we said that though beriberi is commonly regarded as a tropical disease it is by no means restricted to regions with warm climates. In the last decade of the nineteenth century there were several reports of it in temperate climates ; a few of these may be mentioned. Peripheral neuritis associated with beriberi was noted as occurring in 1894 among inmates of the Suffolk County Asylum, Melton, and in the same year at the Richmond Insane Asylum, Dublin. In the latter there were 174 cases of whom 127 were males and 47 females ; the inmates only were affected, none of the staff, and the symptoms present comprised œdema, cardiac irregularity and paresis of the leg muscles. The fatality rate was high, 14·3 per cent.

In the following year it was observed in asylums in the United States, in Alabama at the Tuscaloosa State Asylum, and in Arkansas at the Little Rock Asylum. In 1896 it was again noted at the Dublin Asylum in epidemic form ; 114 cases in all, but this time in addition to the inmates, 107 of whom were attacked, 31 males and 76 females, seven of the nurses also suffered. In the succeeding year there were 246 more cases, making in the three epidemics which occurred in four years a total of 534 cases, and the fatality rate was 8·2 per cent.

In 1897 beriberi was reported on the Continent of Europe and, as in all the foregoing, at asylums, namely in Germany at the Gräfenberg Asylum, Bavaria, and the Alt Scheritz Asylum, Leipzig, Saxony. The same year it was reported among Newfoundland

fishermen and on board sailing vessels travelling from New York to Shanghai and only among the officers, not members of the actual crew. It was remarked that the vessel had not called at any ' beriberi port ' and also that the accommodation was good and the diet varied. The fact that the officers suffered whereas the crew escaped ruled out overcrowding, and the diet being a varied one it was thought that the illnesses might be due to some special article, possibly some poisonous constituent. Two officers persisted with the diet and both died ; the others gave up the cabin diet and took instead maize meal, stale bread, molasses and condensed milk and recovered. The question of causation is dealt with below.

THE CAUSATION OF BERIBERI. I. EARLY VIEWS

The historical interest of this disease rests in the suggestions of the early days and the scientific experimental work of the more recent to clarify and prove its ætiology.

The early ideas in this, as in most diseases and not only those of warm climates, were mere statements, suggestions without proof, each based solely on the *ipse dixit* of its author. These call for little more than mention and need not be considered seriously. Thus, Féris, in 1882, held that beriberi was of the nature of a *rheumatic process*, a disease associated with chill, brought about by hot and damp weather with great fluctuations in temperature ; others, among them Christie, Morehead, Carter, van Overbeck de Meijer and Laoh, that it was closely allied to *scurvy*. It is true that both being, as we now know, due to vitamin deficiency, they often occurred together and so might be confused or even thought to be different manifestations with the one cause.

In 1862, Evezard of Madras, who later was supported by Lodewijks of the Netherlands Indies and by Schutte, regarded it as a kind of *pernicious anæmia* and Pereira of Bahia in 1881 elaborated this as a " dystrophic depending upon insufficient oxidation of the blood, induced by a variety of debilitating influences." But the anæmia, whether brought on by the disordered nutrition, as Pereira hinted, or otherwise, is an essential part of the disease ; van Leent (1880) however definitely regarded abnormal nutrition as primary and the anæmia as secondary and not as ' idiopathic.'

We need refer to one more only, namely *malaria*, and in countries where all ills were at one time or another ascribed to malaria it could not be expected that beriberi would be an exception. We find Heymann in 1855, van Hatten in the Netherlands Indies in 1858, Swaving in the same country in 1870, Roe in the British

Army Report for 1869 and Barry in that for 1870, Clapham in 1872, Russell in 1881, and others in India and Ceylon, and Simmons in 1880 in Japan, supporting this view. It is, of course, true that malaria and beriberi may occur in the same districts, but the symptoms of the two differ widely and there are foci where malaria is intense but beriberi is not met with, *e.g.* Orissa, the Ganges Delta, parts of the China coast, and of tropical Africa. The idea was fostered by the observations of some practitioners that there was greater prevalence on the sea-coast and along river-banks where the soil was swampy and malaria prevalent.

These suggestions were put forward more by way of accounting for the nature of the condition than ascribing them as causes, and the latter will now be considered in more detail.

At first the reasons adduced for a disease which was known to be endemic assuming epidemicity were of the vaguest. *Climate* itself was mentioned, not as of direct causal significance, but it was noted that *season* appeared to play a part in its becoming epidemic. Such outbreaks were noticed to occur in the rainy seasons in Japan, India (Madras), Brazil and elsewhere, and to die down again with the oncoming of the cold and dry season. *Soil* was thought to play a more effective part, since the disease was observed to be more prevalent on the coast and along river-banks, and early observers such as Marshall in 1822 and Hamilton, four years later, had stated that a removal of some 40–60 miles from the coast was sufficient to give immunity, and Malcolmson, a decade later (1835) in his treatise on beriberi confirmed this by his own experience, but wisely added : " This law will, I have no doubt, require to be greatly modified as our information is extended," and in a very short time exceptions were reported. Thus, Balfour in 1847, when analysing cases of beriberi among troops in the Madras Presidency for the ten years 1829–38, found that of 1116 cases 394 were on coast stations, 537 on the plains 40 miles inland, 132 between 40 and 100 miles from the coast and 53 on high ground over 1300 feet above sea-level, though there were only two such stations, Secunderabad and Kampti, and the force there was small. Later, Kearney in 1872 in Madras and Burma, and Fayrer in 1880 in Assam reported cases hundreds of miles up-country.

White races, according to earlier figures, seemed to enjoy a certain degree of immunity. Europeans and Americans were observed to suffer much less often than natives. It was noticed that, in epidemics among a mixed population, the natives or coloured immigrants were attacked in far higher proportion than

the whites, who might indeed escape altogether ; Ondenhoven, as long ago as 1858, remarked upon this in the Dutch East Indies, and he was not the only one ; Praeger recorded the same six years later. Among the very poor whites, as in Amboina in 1858, the disease was as frequent as among the natives. Van Leent in 1880 analysed the cases among the crews of the Dutch East Indian squadron for the period 1870–77, and found that the relative incidence among Malays and Europeans was as 60 to 1. Balfour, whose figures for Madras have been mentioned above, noted that between 1829 and 1838 only two cases were seen among the European troops in the Presidency, and Fayrer later, in 1880, stated that in the Calcutta outbreak of 1878–80, which invaded the suburbs also, Europeans escaped entirely. Ridley in 1818 wrote of its rarity among Europeans in Ceylon and Marshall in an article published four years later on the Medical Topography of Ceylon stated that he had never seen any but the blacks suffer from it. Similarly, in the West Indies, Larrey in 1867 and Minteguiaga in 1874 stated that they had not observed cases except among the negroes and the Chinese. E. B. Vedder summed up the evidence more recently by saying that Europeans are rarely attacked even when surrounded by natives suffering from the disease, but that this freedom was not due to lack of susceptibility because inmates of prison camps, of asylums (see above) and sailors on a long voyage and living on an ill-balanced and monotonous diet may develop it.

Most, if not all, of the earlier writers on this disease, some of whose names have been already mentioned—Christie in Ceylon, Rupert in Borneo, Heymann in the East Indies, Wernich and Simmons in Japan, Larrey in the West Indies, Pereira in Brazil —have noted the fact that beriberi was much more common among males than among females, and some go even farther and state that female cases were rare, though pregnancy or other debilitating condition might render them more susceptible. The fact that the strong or apparently robust man was more prone to be attacked than the weakly was noted with surprise [we can understand it now because the stronger would eat more] ; one example will suffice. Rupert writing in 1880 concerning an outbreak in Sumatra says

So far as relates to constitution the fact was brought out [among prisoners attacked] that there were no doubt a few weakly individuals among the patients, but that the great majority were strong persons between the ages of twenty and thirty, and that it was often actually the strongest and best nourished who were attacked.

Simmons and Baelz in the Tokyo outbreak of 1881 noted that among 626 patients treated 593 were of a robust type, 27 of moderate build, and six only were weakly.

Age, again, seemed to play a part ; we shall refer later to the so-called infantile beriberi, but excluding this for the moment, it was generally observed that children and the aged often escaped, while those in the prime of life constituted the vast majority of the victims.   Thus, Scheube noted in the Kyoto epidemic of 1881 that of 581 patients treated by him only 35 were children, and of 933 at Tokyo, 15 or 1·6 per cent. were between 10 and 15 years of age, 753 or 80 per cent. were between 15 and 30, 89 (9·5 per cent.) between 30 and 40 and 76 (18·1 per cent.) over 40 years.   Children, however, were not exempt and outbreaks have been recorded at Orphanages, as at Samarang in 1864–5 and at Toukiji in Japan.

It was further stated that *length of residence* in a focus of the disease seemed to play some part. From estimates made by Calhoun in Ceylon and by Hamilton and Malcolmson in Madras, among others, " a stay of some months on the station is almost essential for the production of the disease and the greatest predisposition exists when troops have been about eight to twelve months in the settlement."   In this connection it is interesting to note that Stanton's researches subsequently showed that symptoms usually began to appear after three months' living on the polished rice diet (see below).

Occupation also seemed to be of importance and those in comfortable circumstances [in rice-eating countries] were sometimes more seriously affected than the working classes. This we can now explain by the fact that the better classes would consume more of the polished rice, the poorer would eat the coarser, less refined quality.   Scheube in Japan observed that even the highest ranks were not exempt and that most of the patients belonged to what are now classed as sheltered trades—" scholars, priests, merchants, artists and handicraftsmen "—and Féris in 1881, writing in *Arch. de Méd. navale* on Beriberi in Brazil, says : " On voit quelquefois l'affection attaquer les personnes qui sont dans une position élevée ; on peut dire que, jusqu'à présent, aucune position sociale n'a été respectée."

Seeing that the disease prevailed in certain gaols, in asylums, on board transports and coolie ships, it was naturally thought that *overcrowding* and bad ventilation played a part in the ætiology, and were vaguely spoken of as " fouling of the air by noxious matters, such as investigation cannot discover with precision," as Rupert expressed it.

2. ÆTIOLOGY

(i) Parasites, Contagion, Bacteria

During the last quarter of the nineteenth century these vague generalizations began to be replaced by suggestions of a more specific ætiology. Among the earliest of these was that the disease was *parasitic* in origin. Gelpke in 1878 compared beriberi with trichiniasis, but in place of measly pork the food conveying the infection was thought to be dried fish which entered largely into the diet of prisoners in the East, the fish being imported from China. " The diffusion of the disease," he said, " extends to every place where the fish is caught and eaten ; it breaks out in epidemics wherever the fish comes in its migrations . . . or wherever its poisoned flesh is introduced by commerce."

Four years later another helminthic parasite was thought to be the cause ; Erni regarded it as an affection of the intestinal mucosa due to *Trichocephalus dispar*, or *Trichuris trichiura* as it is now called. He found the worms sometimes at autopsies and at other times " small round worms." His description is poor but it is not unlikely that he saw hookworms and, incidentally, hookworm anæmia and œdema bear some resemblances to wet beriberi. Wucherer and da Silva Lima in Brazil found " small worms resembling *Ancylostoma duodenale* in the bodies of several persons dying of beriberi."

Van der Scheer in 1900 expressed the opinion that the disease was caused by a parasite living in the intestine and producing a toxin. He even went farther and suggested that outside the human body its host was *Blatta orientalis*, the cockroach. His theory was that this insect is present wherever there is beriberi ; that it *may* feed on human excreta, and man *may* become infected by Blatta excrement ; further, that part of the life-cycle of the [hypothetical] parasite *may* be passed in the body of the cockroach —hardly a theory at all, but pure supposition from start to finish. Further disproof was afforded by H. M. Joint who, describing an outbreak of beriberi in Fiji, remarked its prevalence among Japanese coolies although they and their dwellings were cleanly whereas Indians alongside of whom they worked were uncleanly and lived in quarters swarming with cockroaches, but contributed no cases of the disease.

Equally vague was the surmise of P. T. Carpenter whose opinion, however, is entitled to respect as one who had had wide experience of the disease in British North Borneo. He wrote in 1899 that there is " a germ of some sort in the exhalations of the

soil of the district where beriberi is endemic that may actually, *per se*, cause the disease in predisposed subjects." The predisposed are the poor, ill-fed, ill-housed, and often overworked coolie, or, in endemic sites, inactivity, confinement to bed, any debilitating cause render the subject liable. Manson's view was nearly allied, in ascribing the disease to inhalation of poisons from the soil or walls of infected houses.

A reflection, or recrudescence, of this "germ in the soil" theory cropped up more than twenty years later in a paper read at the Third Medical Congress of Venezuela in 1921. It was entitled : *Beriberi. Su historia en el Estado Apure ; primera aparición ; epidemias.—Su extensión actual ; poblaciones atacadas.* From this we find that the disease was unknown in Apure prior to 1886 when it was introduced by traders from Guiana. After an interval of six years it again broke out in epidemic form. In 1913 there was a severe epidemic and neighbouring districts also reported outbreaks. This continued with varying intensity till 1918, the worst year being 1916. It showed certain peculiarities as compared with the general knowledge of the disease up to that time ; thus, the sexes were affected equally, but females with greater virulence ; the white population and recent arrivals suffered most. As predisposing causes malaria, intestinal parasites and post-operation debility were particularly noticed, while the chief exciting causes were insanitary dwellings—damp, dark, dirty and ill-ventilated—and overcrowding such as occurred in the hospital, the prison and the inns, especially the last if damp and insanitary. Recrudescence of the epidemic was observed after the rains when streams overflowed and the ground became saturated. The diet of the people was a mixed one with a tendency to excess of nitrogenous constituents ; rice accounted for only a small part. The author of the paper, Dr. de Milita, asserted that "the parasitic nature of beriberi is indisputable" and that the germ lives in the soil and subsoil of the place infected ; he stated dogmatically that it was not communicable from person to person, nor by the bites of insects, but that the patient carries it on his feet and infects the soil of any locality he visits ; fresh cases arise from this soil infection. Disinfection of the cells of the prison and of rooms was useless and those rooms to which the occupants were sent while the disinfection of the former was being carried out became in turn infected. It was claimed that spread of the disease was prevented by replacing the soil of the hut with fresh sand, every three or four days sweeping it up and re-spreading it after exposing it to the rays of the sun. A possible explanation of

these unusual views would be that the patients were suffering from ankylostomiasis, but there is nothing in the paper to indicate whether this was so or not.

To return to the end of last century and the early years of the present. The idea of infection was fairly widely held. In 1899 Dr. Francis Clark of Hong Kong reported an outbreak among the children in an asylum for the blind under circumstances which, with the state of knowledge of the disease in those days, would appear to lead to a natural and well-founded inference. These children attended divine worship at a neighbouring home for foundlings, where many Chinese lived. A few of the asylum children suffered from beriberi. In five months sixty-nine out of 102 children in the foundling home were down with the disease, all between four and seven years of age. The two establishments had a nurse in common. The infection theory seemed fully justified. There was no question of a meagre diet ; the rooms were dry, well lighted and freely ventilated, and sanitary arrangements were satisfactory. All those who were attacked slept on the ground floor.

Dr. D. C. Rees, in 1898, was a supporter of the theory that beriberi was a ' place ' and not a ' food ' disease. He noted its occurrence in outbreaks where there was overcrowding as in asylums, in ships, in barracks and coolie quarters on plantations, and remarked that removal from an infected environment, such as leaving the ship and entering hospital, was followed by rapid improvement and recovery ; he overlooked the fact that this implied in most cases, if not in all, a change of diet also.

Cantlie was another who regarded the disease as communicable, stating, in 1902, that in a general ward in Hong Kong where beriberi patients were being treated, those with open sores contracted the disease while others escaped. Waterhouse also, in the *Army Medical Record* of 1902, considered that the disease was a place and personal infection and that diet had little to do with its propagation. He instances a prison with a hundred inmates where no cases were observed until two patients were brought in, after which there was a steady increase. Stanley of Shanghai was another who favoured the idea of contagion and did not believe that rice played any part. Among prisoners at Shanghai he noted that it was the long-sentenced men who suffered.

It is but a short step from the suggestion of contagion and infection to that of specific bacterial agents. It will be convenient to consider this here, though chronologically the ' diet theory ' preceded it. From quite early days beriberi was ascribed to

monotonous and deficient diet, but not on any specific grounds, merely as a vague conjecture, and, as the notion of bacterial origin developed with the science of bacteriology, opinion that diet was a major cause fell more into the background.

Bacteria were looked for in the excreta, fæces and urine, in the blood, and in the tissues. With the crude technique then employed it is not surprising to hear that organisms were found. Later, when more care was taken, the blood always proved to be sterile and none of the organisms isolated from the excreta fulfilled Koch's postulates (on which much stress was laid at the time), nor did injection of them reproduce the disease in experimental animals and—most important of all—different investigators isolated different organisms.

One of the earliest bacteria thought to be the cause was a *Staphylococcus albus* which Hunter, in the *Lancet* of 1897, stated had been found by Pekelharing and Winkler in all cases of beriberi. He stated further that when this was injected into animals it produced a neuritis similar to that of beriberi and he concluded therefore that it was the actual cause of the condition. The same organism was also found in the rice used for food ; Hunter accordingly supported the 'food' and not the 'place' as the origin of the disease, but the food *viâ* the coccus. Sambon in 1902 expressed much the same opinion ; he regarded rice merely as a vehicle of infection on which a micro-organism develops under certain conditions and in certain places ; that this organism lives within the human body, being introduced by food. Manson the same year formulated his hypothesis in some detail thus :

I hold that this neuritis is produced (*a*) by a toxin, (*b*) the product of a germ operating in (*c*) some culture medium (*d*) located outside the human body. Further, I hold that (*e*) the said toxin enters the body neither in (*f*) food, nor (*g*) water, and am thereby forced to conclude that it is introduced (*h*) through the skin or (*i*) that it is inhaled.

Tsuzuki in 1905 claimed as causative a diplococcus isolated by him from the urine and fæces of patients, but not from their blood. The organism, which he named *Micrococcus beribericus*, was 0·7 × 0·4 micron in size, Gram-positive, non-motile, fermenting glucose and lactose without gas production, causing clotting of milk after a week, resisting a temperature of 60° C. for an hour. On agar it grew as small, semi-transparent colonies.

H. Wright, an ardent supporter of the bacterial origin, but of a bacillus, not Tsuzuki's diplococcus, stated his views in 1906 as follows : Beriberi is an acute infectious disease caused by a specific

bacillus. The course of symptoms set up is that of acute poisoning of the nervous system, preceded by gastro-intestinal disturbance, vomiting, gastro-ectasis and perhaps diarrhœa. The toxic symptoms arise from absorption of the specific ' virus ' and include anæsthesia, flaccid paralysis, œdema and cardiac dilatation. In acute cases the acme of the poisoning occurs between the twentieth and thirtieth days, and the syndrome *plus* the acute poisoning constitute beriberi proper. At this stage the peripheral terminations of the neurones show no signs of degeneration, but if the condition passes on to a chronic stage degeneration of true Wallerian type takes place and there is residual paralysis. Wright stated that a bacillus is constantly present, but Dudgeon, who made a study of this organism, found that it had no action when injected *into animals and that it was not agglutinated by the sera of beri-beri patients.* Tsuzuki, on the other hand, claimed that in dilutions up to 1 in 50 the sera of 103 out of 106 beriberi patients agglutinated his micrococcus whereas none of 26 controls did so, and also that injection of the soluble toxin of his organism produced in animals the same changes as those seen in human cases of beriberi, namely cardiac and paralytic lesions.

Two years later Tsuzuki was still advancing claims calling for recognition of his *M. beribericus* as causative. He considered that the ' rice intoxication theory ' was disposed of by the report of two divisions of the Japanese army living under practically the same conditions and using the same rice. In one there were 1127 cases, in the other only 161, and he attributes the spread of infection to soldiers returning from active service.

Next for consideration comes an organism with a peculiar history, for only secondarily was it believed to be concerned with causing beriberi. In 1919 P. Noel Bernard was studying at the Pasteur Institute, Saigon, ' climatic fevers ' ; by blood culture in cases of beriberi he isolated from 61 natives and 31 Europeans a large motile Gram-positive, spore-bearing, ærobic bacillus which liquefied gelatin, hæmolysed red corpuscles and fermented—giving acid but not gas—maltose, saccharose and glucose, but not acting on lactose or mannite. The patient's serum, he found, contained agglutinins for it and it would deviate complement. From fatal cases Bernard isolated it from the spleen, liver, kidneys, and brain, and, when inoculated into rats, it produced a hæmorrhagic, gelatinous œdema and general septicæmia. He suggested the name *Fièvre astheno-myalgique* for the fever associated with its presence, though he did not claim that it was actually the cause of the fever. Later examination showed it to be pathogenic for young pigs,

rabbits and mice, and to produce in them the same toxic symptoms as in man, and the same organism was often found on rice. In 1921 Bernard named this organism (which had affinities with *B. megatherium* of Bary, 1884, morphologically and in its reactions) *Bacillus asthenogenes*, because of the symptoms associated with its presence. In pigs it produced paresis, even paralysis, in six to seven days and death in six to fifteen days, and passed from the intestine into the blood and tissues. The organism was found in nature in rice and soil. In some cases the symptoms produced were those of dry beriberi and the disease was acquired by animals fed on polished rice infected with the organism obtained from a human case. But as the characteristic symptoms of beriberi and the presence of the organism occurred in piglets fed on polished rice and not in those on whole rice, it would be inferred that the bacillary infection was of a secondary nature. Pursuing his investigations Bernard affirmed in 1925 that beriberi was due to fermentation set up by his organisms and not to vitamin B deficiency. He carried out further complement fixation tests with sera from 131 natives, of whom 76 were beriberi patients in hospital. For antigen he used a filtered culture of *B. asthenogenes* grown anaerobically ; he found the maximum production of toxin to occur under such conditions. Of the 76 cases a positive reaction was obtained in 50, whereas in 55 cases other than beriberi 53 were negative. He maintained, therefore, that the reaction had considerable value in confirming the suggested relationship between *B. asthenogenes* and beriberi.

José Montés carried out further studies on what was probably the same organism in the Philippines in 1926. From the pleural exudate of some adult patients and from the bodies of children recently dead of the disease he cultivated an organism which " conformed to the morphology and reactions of *B. mycoides* or *B. mesentericus*." Inoculation of cultures into monkeys and cats caused death with lesions similar to those found in the children and a vaccine standardized to contain 1000 million per c.c. was given in doses from 0·25 increased to 1·5 c.c., and of 400 patients so treated 72 per cent. were said to have been cured and it was reported as being useful to women in pregnancy as a preventive of infantile beriberi, but no mention is made of controls, so that the value of these reported successes must be discounted.

In 1929 A. Cannon, in an article in the *British Medical Journal,* reverts to the bacillary theory in part and ascribes beriberi to three factors : Deficient vitamin B, *B. asthenogenes*, and endocrine disturbance. The organism, he stated, could be isolated from the

blood and cultivated in a medium of bouillon and milk under anaerobiosis ; that it was agglutinated by the sera of patients which also gave the complement deviation reaction.

With this exception, for some years after Montes' work we hear no more of this organism, but in 1933 André, having studied cases in China, concluded that avitaminosis alone would not explain the disease, and " a study of such cases, as seen for example in an outbreak at Hankow in 1929, shows clearly that it has the characteristics of an infective malady," also that Bernard's *B. asthenogenes* is responsible for the toxic infective character of beri-beri, and acts more powerfully when there is lowered resistance from any cause, one such being a diet deficient in vitamin B. André held that three factors' were concerned in the ætiology, namely the infecting organism, *B. asthenogenes*, gastro-intestinal disturbance associated with carbohydrate fermentation, and a lowered resistance.

In 1929 Japanese investigators brought forward another bacillary claimant which was known as Matsumura's *B. kakké*, or *B. beriberi*. It resembled *Bacterium coli communius* and was found in the intestine of human cases and of experimental animals, but differed in giving agglutination and complement fixation which the *coli* organism did not. Matsumura and his co-workers found it in the fæces of 98 out of 135 human cases (74 per cent.), whereas it was found in 1 per cent. only of non-beriberi cases, and they concluded that it was " the principal ætiologic factor in experimental beriberi." The following year Vianna and Pedro studied six cases of the disease among prisoners in Nictheroy, Brazil, and from the fæces of one isolated Matsumura's *Bacillus kakké*. This patient's serum agglutinated the organism in a titre of 1 in 400, but *Bacterium coli communius* in 1 in 100 only. The serum of another patient, although the organism was not isolated from him, agglutinated the *Bacillus kakké* at 1 in 100, but the *coli* organism not at all. Experimentally, the organism was isolated from two cases of polyneuritis columbarum as well as from the human subject recorded. On the other hand, de Araujo, investigating cases in the asylum and the State gaol of Bahia, Brazil, concluded that, though Vitamin B deficiency was not the cause since the diets were not poor in this vitamin, the organism of Matsumura was not the cause, judging by agglutination tests.

Finally, in 1932, M. Ramos of Pernambuco reported the results of over 6000 agglutination tests with this bacterium and the sera of beriberi patients and others. The organism was isolated from 25 out of 36 stools examined and it was agglutinated by the sera

of the patients, but of 50 normal healthy subjects 25 also agglutinated it and he concludes that the organism is not, therefore, specific of beriberi.

Hirsch, more than fifty years ago, in 1885, summed up the position with his usual acumen and saw no reason for regarding beriberi as infective. He states :

> It appears to me to be doubtful whether the disease is to be reckoned among the infective diseases properly so-called ; and I hold it to be still less justifiable, in regard to the etiology, to give way precipitately to the modern craze for bacteria in this particular field of enquiry, or to seek to establish the *communicability of the disease* on the ground of casual and ambiguous facts. From India and the Malay Archipelago we have not a single fact affording certain proof that the disease is transmissible ; while, against the idea, there is the fact that beriberi continues to be endemically prevalent in India at the present day within the same narrow limits to which it was confined at the beginning of the century. When it has broken out on board ship among Indian coolies, it has never spread to the attendants of the sick, the sailors and others ; and the observation of practitioners in Brazil are just as decidedly opposed to the importation or transmission of it by means of individuals or by goods.

(ii) Food

In the opening years of the present century the question of the cause of this disease was in a very nebulous state and it was but natural that the suggestion should be made that " every avenue should be explored," if we may be pardoned the anachronism of using a political term of more than a quarter of a century later. So we find Max F. Simon calling for more detailed study of the blood of beriberi patients for proof of infectivity, presence of organisms, chemical analyses, and comparison of the results with those of non-beriberics.

The presence of peripheral neuritis was the notable feature in beriberi and the arsenic poisoning outbreak in Manchester and elsewhere in England in 1900–01 made people think of beriberi as being possibly a metallic toxic neuritis, perhaps arsenical, but more mature consideration of the differences soon demonstrated the fallacies. Nevertheless, in 1902 Ross was still toying with the idea and apparently obtained some confirmation, for he recorded in the *British Medical Journal* that he found arsenic in the hair of twenty-one cases of beriberi in Penang and Adampur and in several reported from Singapore.

Others postulated either a food toxin introduced from without, or auto-intoxication, such as might be produced from fermentation or bacterial growth in the intestine, as noted when speaking

of Bernard's organism. Rice being known to be closely associated in some way with beriberi a rice poison was looked for and Japanese workers extracted from polished rice by means of alcohol a substance which they called *oryzatoxin*. This when given to birds and mice with their food caused no disturbance, but when injected subcutaneously gave rise to weakness, loss of weight and paralysis, ending fatally. If, however, an adequate supply of Vitamin B was present in the diet paralysis did not occur. There is no need to detail the various experiments, for the results varied and no conclusions of value were reached, except that whether ' oryzatoxin ' was given or not the symptoms were obviated by a diet containing the missing vitamin. In 1885 Takaki had reported that beriberi had been abolished from the Japanese navy by dietary changes, substitution of barley water for polished rice.

With beriberi, as with most diseases whose causation was obscure, improper food or drink, or deficiency of the former, has for long been suggested. ' Tainted water ' was an idea brought forward by Wright in 1834, more than a century ago, or, if cases occurred near the coast, ' brackish water.' The suggestion was contradicted by Malcolmson the following year and by Richard in 1876, among others. This may be mentioned in passing ; it has now no importance.

Insufficient diet, or a diet inadequate qualitatively and, in certain constituents, quantitatively as *a*, or even *the* causative factor has held the field for three-quarters of a century at least. That rice was the chief article of diet concerned was a fact present to men's minds for a long time before it took definite shape, and, on the other hand, cases were at times reported in which rice played no part. The idea that the exclusive or preponderating use of rice and of dried fish, deficient in albumen and fat, was fundamental in the ætiology of beriberi was of gradual growth. Overbeck de Meijer in 1864 remarked the prevalence of the disease among sailors whose diet consisted largely of salt meat, and among soldiers who had to subsist largely on local food (rice) of the country where they were stationed. Kappen, a year before de Meijer, had noted that Chinese working in the Banka Mines who lived well and had a varied diet, remained in good health, while others on an insufficient diet, or a monotonous one, developed beriberi. Werthoff in 1879 noted its presence among employees of the Dutch East Indies service whose diet was chiefly rice and dried fish, and much of that not of very good quality, and the same year Schutter reported it among prisoners at Paramaribo, who lived on rice, salt fish and boiled green bananas.

Gradually the 'rice theory' gained in importance. Thus, Wernich, also in 1879, when speaking of beriberi as he saw it in Japan, maintained that rice, as the exclusive food of the people, was responsible for the disease, not because it was decomposed [he was then anticipating subsequent theories] but because it was used in such quantities that " the power of assimilation is gradually lost for other kinds of food." That mere insufficiency of food was not capable of causing the disease was noted by several observers, Waring and others, who showed that in times of famine beriberi was not more common than in times of plenty. More important, but at the same time more puzzling, was the observation of Rupert in Borneo in 1880 that among troops and crews beriberi was rife although these had " twice a week fresh beef, poultry, eggs and coffee, besides fish, salt meat, potatoes and rice ; whereas the labourers of the country whose food for long periods was nothing but rice and a piece of dried fish, were entirely free from the disease." We can only explain this by assuming that the latter had whole rice whereas the former had refined, polished or decorticated rice. Malcolmson supported this and added that if the disease was due to rice it would be practically general over India and the East Indies. In Brazil also the theory gained no credit because the disease was common among the better, the proprietor, class, people who lived in comfort and even luxury. Féris, in 1881, summed up the position in these words :

Comment se fait-il que les individus les plus atteintes soient ceux de la classe élevée plutôt que ceux de la classe inférieure qui, luttant avec la misère, s'alimentent mal ou insuffisament, et pourtant sont précisément ceux qui payent le moindre tribut à l'épidémie ?

Much investigation of beriberi has been carried out in the Netherlands Indies dating from this time. In 1886 a Dutch Government Commission was created in Java largely owing to the increase of cases in the army in the course of the Achin War. At first the patients were sent from Achin to Weltevreden and when the hospital there became overcrowded to Kampong, Macassar (Celebes). In 1875 there was at Batavia accommodation for 150 beriberi cases ; in 1880 there were 818. Barracks for them were built at Buitenzorg for 150, and by April that year there were 370 cases there. The Netherlands Government, as stated above, delegated Professor C. A. Pekelharing and Dr. C. Winkler from Utrecht to investigate and, if possible, to determine the cause. They began their studies in November 1886, at Batavia, passed on to continue them on Achin at Kota Radja, and then returned to Batavia. In 1887 they published their report that " from the

blood of beriberi patients a microbe could be cultivated which, if injected into rabbits, caused degeneration of the nerves which could be considered to be analogous to that found in corpses of beriberi patients."

The same organism was found in the soil and in the air of the barracks, so as thorough disinfection as was possible of these was recommended. A laboratory was established in Batavia for studying the pathology and bacteriology of the disease, and the first Director was C. Eijkman who had entered the service in India in 1883 and had assisted Pekelharing and Winkler. The two latter returned home in 1887. The measures they had indicated proved fruitless ; the numbers of patients on Achin continued to increase and between 1893 and 1896 the extent of the disease and its mortality were frightening. Europeans suffered to some degree, the native soldiers much more, and the native auxiliaries and prisoners most of all. Each boat from Achin to Padang brought two to three hundred beriberi patients who were taken to the highlands—Kaju Tanam, Ula Lima, Manis and Fort de Kock. Improvement when they arrived there was remarkable and rapid ; even on the voyage, which occupied only a few days, amelioration was observed. Some who had to be carried on board when leaving Achin were able to walk off on arrival at Padang and so marked was this that a suspicion of malingering arose, but was dispelled when reduction of evacuation was seen to result in speedy increase in deaths. It was naturally believed that overcrowding was the main cause, and general depression from the conditions of the life a close second.

Among the annual reports from the laboratory came an important one by Dr. Eijkman in 1890 on *Polyneuritis in Chickens*. This was followed by others in the two ensuing years, establishing a relation between this condition, which occurred when chickens were fed on a certain rice, and beriberi in man. He noted that the effect ensued or failed to appear according as the birds were fed on polished or unpolished rice. In 1896 Dr. Eijkman became Professor at Utrecht and Dr. G. Grijns was appointed to succeed him as Director of the Laboratory in Batavia. Grijns, pursuing the investigation, came to regard beriberi as a disease originating in a lack of some indispensable ingredient in the food. Eijkman did not, as is the fate of most scientific investigators, go unrewarded. As a result of his researches in beriberi he was in 1929 awarded the Nobel Prize with Professor F. Gowland Hopkins, and died at the age of seventy-two in 1930, being then Emeritus Professor at Utrecht. Dr. Grijns became Professor at Wageningen.

To complete this part of the story : As a result of the work of Eijkman and Grijns, General J. B. van Heutsz on Achin at once put an end to overcrowding or " life in the concentrated line " ; confinement was stopped, food supplemented by fruit and herbs, and beriberi from that time began to decrease.

In the course of the work which had been carried on in Batavia an outbreak of polyneuritis arose suddenly among the experimental fowls. This was for a time most puzzling and it continued for nearly five months and was finally traced to the use of boiled rice obtained by a laboratory assistant, for purposes of economy, from the military hospital kitchen. A new army chef arrived who " refused to give military rice to civilian fowls " and the outbreak came to an end.

The laboratory the establishment of which was recommended, as stated above, by Professor Pekelharing in 1887 for the study of medical problems was founded on the 15th January, 1888, as the Research Laboratory for Pathological Anatomy and Bacteriology, with C. Eijkman as Director. In 1910 its name was changed to the Medical Laboratory. On 15th January, 1938, the fiftieth anniversary of its foundation, it was renamed, in honour of its first Director, the Eijkman Institute : the Central Laboratory of the Public Health Service.

In order to give a connected story of the work at Batavia we have somewhat anticipated the sequential order of events and must now retrace our steps a little.

Uchermann is another who, at the beginning of the present century (1902), was an opponent of the rice theory, because cases might arise on ships where rice was not an article, at least a staple article, of the diet. In his opinion the cause was more probably some toxin in tainted food, which might be vegetal or animal. In other cases he thought it might ' arise spontaneously ' on ships, as the disease might not make its appearance until the vessel had been some four months at sea. Laoh, as we have seen, was among those who thought that beriberi might be a form of scurvy.

As a result of his opinion Uchermann suggested as remedies reduction in the tinned preserved foods, increase of fat, the use of potatoes and fresh vegetables when at sea and of fresh fruit when in port, and the filtration of the drinking water.

Schuttelaure was apparently emerging from the wood when in 1902 he recorded two outbreaks at Diego Suarez, one of which was terminated by increasing the fat in the diet of those attacked, and the other by replacing the rice which had deteriorated with age by fresh bread and non-decorticated rice. *A propos* of the

rice controversy Nightingale in 1902 contrasted the prevalence of beriberi in different races regarding their dietetic customs. In Bangkok, he noted, although rice was plentiful beriberi was rare ; among Tamils in the Straits Settlements the disease was quite uncommon and they do not decorticate their rice until after it has been cooked ; while, lastly, the Chinese and Malays in the Straits Settlements suffer severely from beriberi and they are accustomed to eat rice which has been decorticated for a year or longer.

Christopherson thought to throw light upon the question by saying that in his view rice paralysis was distinct from beriberi, the former being due to the action of a toxin. From the clinical and pathological aspect he averred that in rice paralysis the motor fibres are affected more than the sensory, while the vasomotor system is less involved and the heart and vagi are unaffected ; further it does not, he held, appear in epidemics as does beriberi, and the case fatality rate is much lower.

Observations recorded in Kuala Lumpur by Travers in 1902 were very difficult to explain in the state of knowledge at the time. He noted that the inmates of five institutions—hospitals and gaols —were supplied with food from the same source, but in one only did beriberi prevail. Dr. (later Sir James) Cantlie in commenting on this states : " So scientifically and thoroughly was this investigation carried out by Travers that it would seem a flawless and conclusive proof that the specific agent concerned in the production of beriberi is not conveyed by food."

Time showed that several of these apparently contradictory opinions were correct ; the disease was shown to be dietetic in origin but not necessarily associated with the eating of rice. Many articles of food besides rice were demonstrated to be deficient in neuritis-preventing vitamins, such, for example, as fine wheat flour, wheat bread, macaroni, ship-biscuit, sago, etc. Further, when sterilized for canning by heat over 120° C. the beriberi-preventing factor was destroyed. In 1916 Darling showed and diagrammatically represented the overlapping of diseases associated with dietetic deficiencies or avitaminoses—rickets, infantile scurvy, true scurvy, ship beriberi, ordinary beriberi and polyneuritis gallinarum.

Having mentioned the connection between wheat flour and beriberi we may here draw attention to an outbreak in support of it, for it is instructive although it did not occur in a tropical climate, but in Newfoundland. Prior to this the bread was made with brown flour and beriberi was unknown. When pure white

wheat flour came into general use beriberi cases became frequent. In 1910 a ship laden with wholemeal flour ran ashore, and to lighten her some of the cargo was removed and the inhabitants of the adjacent districts consumed it.   During the ensuing year in those areas no case of beriberi occurred.   Aykroyd in 1930 made a study of the conditions in these countries where he saw cases of beriberi, some of them with œdema.   He found that in winter the diet consisted mainly of white bread and tea, there being no meat or fresh vegetables.   Cases of beriberi were most frequent in May.   He observed that the only difference between those
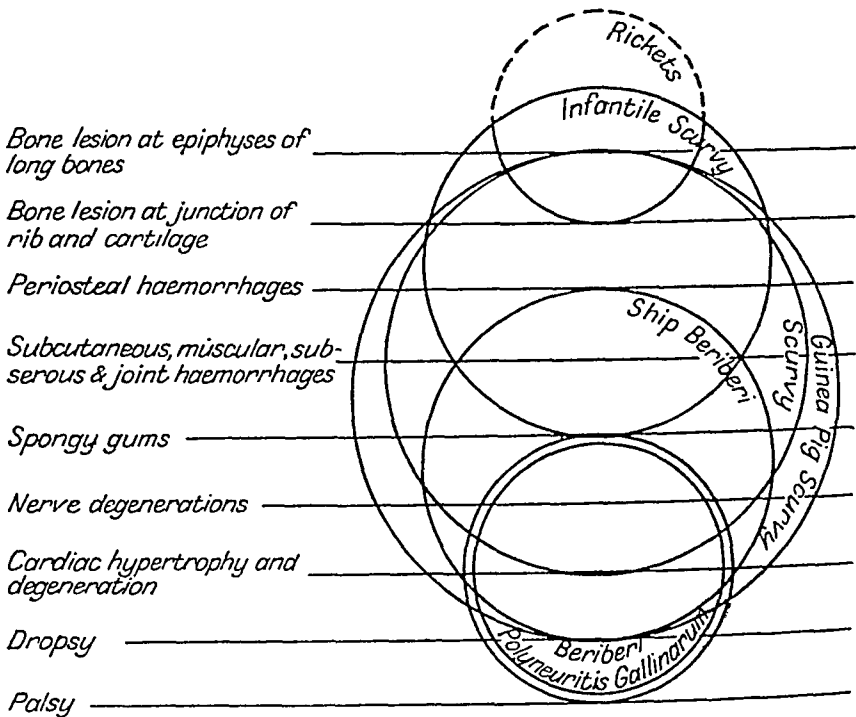
FIG. 12.
Darling's diagram to show overlapping of deficiency diseases.

families in which the disease occurred and those from which it was absent was that the latter were better off and had, in addition to the white bread, meat, potatoes and other vegetables such as peas and beans.

This was by no means the first occasion on which the substitution of white wheat flour had been followed by beriberi. Prior to 1894 Norwegian sailors had biscuit made from rye flour. They then began to clamour for better food and they were supplied with bread made from wheat flour or a mixture of that with rye. Holst, in 1912, reviewing the figures, showed that beriberi ensued and the incidence steadily increased.   The story is told of a captain

who did not approve of the change and insisted on a supply of the rye flour for his own use. .In time the crew were stricken with beriberi and were then supplied from the .captain's store till, in order to preserve his own health, he had to husband what was left.

Some years later, in 1912, C. Lovelace described an extensive outbreak of beriberi among labourers employed in railway construction in Brazil. The form was severe and the case mortality recorded as 15·6 per cent. The diet of the workmen was varied and plentiful, consisting of dry biscuit, dried and tinned meat, with fish, beans and macaroni. Rice was eliminated because of the fear of beriberi ; nevertheless there was a threefold increase in cases in the ensuing year. Fresh meat, onions and potatoes were then included, but even then the disease did not entirely disappear, though some camps suffered more than others.

(iii) Rice and Vitamins

Enough has been said to show that beriberi had within the first decade of the present century come to be regarded as more or less intimately connected ætiologically with diet, or some deficiency in diet ; that, though rice was the food most frequently incriminated, the disease might occur under conditions in which rice was not the staple food, but seeing that in countries where beriberi was most observed rice was the chief food, this was naturally made the subject of intensive study, and we now pass on to describe such of this as has historical interest.

As long ago as 1910, Dr. A. T. (later Sir Thomas) Stanton showed that the method of constructing diet tables needed revision ; that there were factors entering into the composition of foodstuffs of more complex nature than their content in protein, fat and carbohydrate, and their value in calories. It was to these necessary vital principles, as has been already stated above (p. 858), the absence of which from a diet resulted in certain diseases—hence known as food-deficiency diseases—that Funk in 1911 gave the name *Vitamines* (later Vitamins). The theory was not altogether new ; as we have stated already (p. 857), thirty years before, in 1881, Lunin of Basel found that if mice were fed on an artificially compounded milk containing apparently all the constituents of natural milk, as determined by analysis, the animals would not thrive and in time died. Ten years later Socin spoke of some " hypothetical substance " in food, essential for nutrition, and fourteen years later still Pekelharing made a similar observation.

In 1907 William Fletcher carried out an interesting series of

experiments in Malaya, at the Kuala Lumpur lunatic asylum. He obtained rice of two kinds : (i) Uncured ; the ordinary White Rangoon or Siam rice eaten by all classes, except the Indians and Malays, and was the chief constituent of the rations supplied to the inmates. It is husked and cleaned before being sold to the merchants and is stored unboiled. (ii) Cured rice, boiled and dried before being milled ; it is brownish in colour and forms the staple article of diet of Indians and Ceylonese. Native Malays keep their rice stored unhusked and pound and winnow it before use.

Among 120 living on the first—uncured rice—43 cases of beri-beri developed and 18 died ; among 123 on cured rice there were only two cases and both these patients had the disease when admitted. Ten lunatics suffering from beriberi were placed on a diet of cured rice and all recovered, whereas of 26 others not so treated 18 died. Lastly, four inmates who had been on a diet of cured rice for more than five months and were apparently healthy were transferred to a diet of uncured rice, and two of them developed beriberi within three months.

Fletcher's summary is so aptly descriptive of the state of opinion at the time that it is worth quoting in his own words :

. . . at the commencement of the experiment the opinion was held by myself that rice was neither directly nor indirectly the cause of beriberi. It was fully expected that the patients on Bengal rice would suffer from beriberi to the same extent as those who remained on the Siamese variety and that the result of the experiment would be a refutation of the rice theory. With this in view precautions were taken to provide separate cooking utensils, plates, etc., for each set of patients in order that the upholders of the rice theory might not be able to point to any possibility of contamination of the Bengal rice with the poison which is supposed to be present in uncured rice. Contrary to expectation, the result of the experiment, so far as it goes, is to prove the truth of Dr. Braddon's contention that uncured rice is the cause of beriberi. It remains to be proved whether the cause of the disease among the eaters of uncured rice is a poison contained in the rice or whether there is something essential to the human economy which is supplied by the cured rice which is absent in the uncured. Takaki and the Japanese school still hold that a deficiency of proteids in the diet is the cause of beriberi. As yet it has, unfortunately, not been possible to obtain analysis of the two kinds of rice ; but when this is done it will probably be found that the cured rice contains a larger quantity of proteid matter than the uncured. If this be the case the deficiency of proteid matter in the diet may be the actual cause of the disease, or, what is more likely, the lack of nutritive matter in the rice may induce a condition in the patient which renders him an easy prey to some external agency—bacterial or protozoal—which is the actual cause of beriberi.

Fletcher concludes :

Uncured rice is, either directly or indirectly, a cause of beriberi, the actual cause being either (*i*) a poison contained in the rice ; (*ii*) deficiency of proteid matter, the disease being due to nitrogen starvation ; or (*iii*) uncured rice does not form a sufficiently nutritive diet and renders the patient's system specially liable to invasion by a specific organism, which is the cause of beriberi.

Braddon's view was that beriberi was due to ingestion of toxins formed by the action of micro-organisms in overmilled rice which was stored in hot, damp places. It was the suggestion of Eijkman, Grijns and Braddon chiefly that beriberi arose from too exclusive a diet of rice and particularly of overmilled rice—milling bringing about removal of pericarp, aleurone layer and the germ—that led to the classical experiments of Fraser and Stanton in Malaya to which more detailed reference will now be made.

Clearing the ground they started with the basic statement that not only had forms of polyneuritis of different ætiology been denominated beriberi, but even diseases in which neuritis might not be a prominent feature had been included, such as ship beriberi, dropsy, Ceylon beriberi and it was doubtful, therefore, whether any single causative factor would be found to explain all recorded outbreaks.

Among their first experiments were those carried out with Javanese labourers at Durian Tipus, in Negri Sembilan, in 1909, where, by transfer of individuals suffering from beriberi and of whole groups in which the disease was occurring, they were able to test the influence of locality as a nidus of infection and the possibility of communicability of the disease from one person to another ; the results in both cases were negative. They then proceeded to examine the hypothesis of a poison present in rice causing the disease. Rice was washed before being cooked and then exposed to a temperature at or about 212° F. for a length of time sufficient to kill any living organisms. The natural inference would be that if these were the cause of the trouble the time of their activity must be limited to the interval between the milling and the cooking, and further that any deleterious substances produced by these must be capable of withstanding prolonged exposure to moist heat.

The care with which Fraser and Stanton's experiments with birds were planned and carried out merit their being described in some detail, but mention must be made of the fact that twelve years before (in 1897) Eijkman, having observed the disease among the prisoners in the Dutch East Indies where highly milled

rice was used, had fed fowls on the same rice and noted the development of neuritis in three weeks or so ; this neuritis could be cured and even prevented by giving them extracts, alcoholic or aqueous, of the polishings. His view was that the extracts contained an antidote to the poison causing beriberi. Fraser and Stanton carried out experiments with fowls, feeding them on white and on parboiled rice. Birds fed on the former developed polyneuritis. Next, by using various extractives they demonstrated that there was no evidence of any ' beriberi-producing agent ' in polished rice ; the facts suggested rather that removal of the pericarpal layers in the process of milling deprived the grain of some substance of high physiological value. Then followed some crucial experiments on fowls : one group being fed on polished rice, another on partially husked *padi* from which the polished rice had been prepared, and a third on polished rice *plus* the substance which had been removed by the polishing. The results of these proved that polyneuritis in the birds was due to consumption of rice from which the pericarpal layers had been removed in the process of polishing ; further, that such polished rice was equally harmful whether it was freshly prepared or had been kept in store —that is, the development in it of a poison was excluded.

The next step was an examination of the yield in phosphorus, as. P_2O_5, from different kinds and samples of rice, and they found that the phosphorus content may be employed to` indicate the degree of polishing, and the following shows the corresponding beriberi-producing power : (*i*) Polished Siam rice yielded 0·26 per cent. of P_2O_5 and this variety, if used extensively, was usually associated with severe outbreaks of beriberi. (*ii*) Polished Rangoon rice yielded 0·32 per cent. and beriberi was less among those whose diet consisted largely of this form. (*iii*) Polished Malay rice yielded 0·38 per cent. of the pentoxide and consumers of this were still less attacked. (*iv*) Parboiled rice yielded 0·415 per cent. and among eaters of this or of (*v*) Unpolished rice, 0·54 per cent. P_2O_5, beriberi was never produced.

Grijns, Holst and Frohlich had previously shown that meats and vegetables were injuriously affected as articles of diet by exposure to high temperatures. Fraser and Stanton, applying the same test to rice, heated some unhusked rice for an hour in an autoclave at a temperature of 120° F. and fed six fowls on the product ; five of them developed polyneuritis. The value of this experiment was, further, to show the evil of cooking rice by steam under pressure as was done in certain large institutions.

Having shown that the ' protective substance ' was removed

by polishing the rice their next step was to try to isolate this from the polishings. These polishings, they noticed, had a neutral reaction when fresh, but became acid when kept ; this change of reaction, however, did not impair the therapeutic efficiency. Again, ordinary cooking was harmless ; this proved that the essential substance (one or more) is not unstable under usual conditions. Further analysing the polishings, they removed the fat by means of petroleum ether and found that birds fed on polished rice together with the defatted polishings remained well —in other words the fat constituent of the polishings played no part in beriberi (or rather in producing the polyneuritis ; it is well at present not to speak of avian polyneuritis and human beriberi as if they were the same). A large percentage of the phosphorus compounds present in the polishings was found to be soluble in 0·3 per cent. hydrochloric acid ; this fraction was removed from the polishings and birds were fed, one group on polished rice *plus* the acid extract, another on the rice *plus* the residual (exhausted) extract. The latter developed polyneuritis, the former did not ; hence the substances of physiological importance in the polishings had been removed by extracting them with 0·3 per cent. hydrochloric acid.

By further fractioning of the active extract, phytin, which constitutes 1·07 per cent. of unpolished rice, but exists only in traces after the polishing, was removed, and birds were fed on polished rice *plus* phytin ; polyneuritis was not prevented. Further fractionation by means of spirit of different strengths enabled Fraser and Stanton to conclude that the protective substances are soluble in a slightly acid solution containing 91 per cent. of alcohol and they amount to not more than 11·3 per cent. by weight of the rice polishings and not more than one-tenth of this (*i.e.* a little over 1 per cent.) of the original unpolished rice-grain. This fraction includes the alcohol-soluble protein and compounds of calcium, magnesium and phosphorus.

The deduction drawn from these experiments was thus expressed by Stanton in his conclusions (*Collected Papers on Beriberi*) :

In this process [of milling and polishing] there is removed from the grain some substance of high physiological importance in metabolism, the absence of which results in polyneuritis in fowls and beriberi in man when a diet is consumed of which white polished rice is the staple. Whether these substances act by rendering other elements in the diet available for nutrition, or whether they are themselves the nutritive material necessary for nerve tissues can in our present state of knowledge only be matter for conjecture.

Or, briefly, that beriberi is a disorder of metabolism due to deficiency or absence of one or more substances, minute in quantity but of high value in nutrition, present in unpolished rice and removed by milling and polishing.

Though the phosphorus content of rice serves as a standard, as stated above, for estimating the liability of its use to set up beriberi, Fraser and Stanton were careful to announce that:

> In recommending the adoption of phosphorus estimation for purposes of standardization, it should be clearly understood that we do not thereby subscribe to the view that a deficiency of phosphorus in organic combination explains the production of beriberi by the consumption of polished rice ; all the evidence obtained by us is opposed to that view.

Schaumann held that beriberi was due to phosphorus deficiency (see below).

They followed up this experimental work by indicating the preventive means, based upon their researches, for the use of those whose diet consisted chiefly of rice. The chief was, of course, to use unpolished rice, bearing in mind that even good and wholesome rice may be rendered nocuous and productive of beriberi by bad cooking. For those using polished rice and developing beriberi cure could be obtained, in some cases at least, from the use of the polishings ; but since polishings were ordinarily mixed with dust and other adventitious matter, Fraser and Stanton prepared an extract of such strength that 1 c.c. represented the soluble constituents of 10 grammes of fat-free polishings, and they obtained very satisfactory results in cases of avian polyneuritis, and found it also an efficient prophylactic.

For another series of experiments which Stanton carried out on fowls, he obtained from a rice-mill in Singapore (*i*) Rice as it passed from the ' huller ' to the polishing machines, that is, rice deprived of husk only and unpolished ; (*ii*) White polished rice ; and (*iii*) Rice polishings, and he showed that birds fed on the first remained healthy. If, however, this husked rice was sterilized in an autoclave at 120° C. for two hours, the birds feeding on it suffered from polyneuritis, that is the heating had deprived the rice of its protective qualities. On the second product—white polished rice—they developed polyneuritis, but not if the third—the polishings—was added.

H. Schaumann in 1911, working on lines similar to those of Fraser and Stanton, produced in goats a disease associated with paralytic symptoms and closely resembling beriberi. He, as had Fraser and Stanton, produced an extract of rice bran which restored birds and dogs with polyneuritis resulting from avit-

aminosis ; he also obtained like results with extracts of the Indian mung dal, *Phaseolus radiatus*, and isolated a crystalline substance containing nitrogen but no phosphorus ; he believed that the protecting substance was an ' activator ' which produced changes in organic compounds of phosphorus present and concluded that beriberi was due to a deficient metabolism of phosphorus and its compounds.

The following year Edie, Evans, Moore, Simpson and Webster, working at Liverpool, confirmed Fraser and Stanton that alcoholic extracts of rice-meal have protective and curative properties if concentrated under a fan, rather than by means of a water-bath.

More recently de Langen has put forward another biochemical theory, after investigating chemically the tissues of avian and human cases. He believes that the symptoms result from disturbance of lipoid metabolism and failure of synthesis of phosphatides due to lack of vitamin—a theory not very different from that of Schaumann some twenty years before.

Reference to details of the subsequent work of Gowland Hopkins, Harriette Chick, Margaret Hume, Vedder and others on vitamins in Great Britain and the United States would take us too far afield. The work, however, of Strong and Crowell in testing these findings on criminals in Bilibid prison cannot be omitted. They divided their subjects into three groups, all of whom were given the same basic diet, deficient in Vitamin B. In Group I were seventeen persons who were given this basic diet *plus* over-milled rice ; in Group II were six who received the basic diet and overmilled rice *plus* extract of rice polishings ; the third Group, also of six men, received the basic diet *plus* red rice. This diet was persisted with for ten weeks, by which time ten of Group I and two in each of the others showed signs of beriberi, and the conclusion was drawn that serious nutritional disturbances result from a monotonous, ill-balanced diet, which are aggravated if the diet be deficient in Vitamin B.

Casimir Funk, to whom we owe the term ' Vitamine,' investigated in 1913 the properties of the vitamin which he isolated from yeast and analysed it into three different substances, but after trial concluded that in the treatment of beriberi the whole should be used.

In 1926, Jansen and Donath stated that they had succeeded in isolating the vitamin in a crystalline form and analysis assigned it a free base with the formula $C_{12}H_{17}ON_3S$. In Java an acid clay preparation of polishings with pH5 is used and in the Philip-

pines a fluid extract known as 'tiqui-tiqui,' for the treatment of cases of beriberi, the latter particularly for infants.

The question is a complex one and problems in connection with it still await solution. The conditions under which the rice is grown, in particular its water-supply, are factors in determining the endemicity of beriberi. Rice grown on puddled fields on which a layer of water is allowed to remain has nearly one-third less nutritive value than the same rice grown under dry rain-fed conditions.

Great advances have accrued to our knowledge of avitaminosis and particularly of beriberi from the discovery of the close relationship existing between polyneuritis in birds and the human disease. Both result from deprivation or deficiency of antineuritic vitamin ; the problem is not so simple as used to be thought, the two, though similar, are not identical. McCarrison in 1928 (*Indian Medical Research Memoir No. 10*) pointed out that there was a difference between polyneuritis in pigeons and beriberi in these birds, and Graham in 1927 affirmed that beriberi is not due to *absence* of the vitamin but to *insufficiency* of it and, further, his opinion was that such a degree of insufficiency occasioned within the organism the production of a poison which exercises a specific action upon the heart. In support of the former of these propositions he adduced that a diet of decorticated rice gave rise in pigeons, not to true beriberi but to polyneuritis. If dhal arhar (*Cajanus indicus*, a yellow pea habitually consumed by rice-eating peoples) were added—absence of Vitamin B replaced by insufficiency—beriberi results. Also Professor J. C. Drummond and his colleagues have found by experiment on pigeons that some at least of the symptoms hitherto attributed to Vitamin B deficiency were in reality the results of starvation.

This question of the relationship between avian polyneuritis and avian and human beriberi is of sufficient importance in the history of beriberi and vitamin research to warrant a somewhat fuller account. The point has been studied by G. Grijns, H. Schaumann, E. B. Vedder, W. B. Chamberlain, C. Funk, and R. McCarrison among others. At first and, in fact, for some time the polyneuritis of birds was thought to be the analogue of human beriberi, but subsequent research showed that the problem was not so simple and it became still more complicated when Vitamin B was shown to include more than a single factor and that in an ill-balanced diet various deficiencies may play a part. In other words beriberi is of the nature of a syndrome. Clinically, avian polyneuritis and beriberi in birds are not distinguishable, but

pathologically there are marked differences. To discuss these would be beyond the scope of the present work ; suffice it to say that McCarrison regarded polyneuritis columbarum as a true ·deficiency disease and beriberi as a deficiency condition with a super-added toxic factor. It is true he found no toxin in the rice, but he postulates a metabolic toxin, like that of ketones in diabetes. The suggestion of a toxin was not new ; it had been made by Eijkman in 1897, by Mott and Halliburton in 1899, by Stanley in 1903, by Hamilton Wright and by Braddon in 1905, and others.

In 1927 the toxin theory again came to the fore. The disease being more prevalent in the wet season, it was thought that this might be due to stored, damp, deteriorated rice, or to the growth of moulds and a toxin produced by them. Again, investigations carried on in Malaya, at Kuala Lumpur, did much to solve the problem. Heavy rains early in the year washed out the market gardens and a severe drought later led to a further shortage of fresh vegetables. Since the Chinese use mostly polished rice they obtained their Vitamin B from vegetables, and shortage of the latter was followed by marked increase in cases of beriberi. Against the theory of a toxin developing in sodden rice was the experience on two rubber estates. On one the stocks of rice were sodden for several days, while the employees lived on launches or rafts. When the floods subsided vegetables were distributed from gardens which had escaped and no beriberi developed. On the other the rice was kept dry throughout the floods, but the vegetable gardens being washed out this food was not obtainable and beriberi developed.

Rice is clearly the main factor for, as a result of the scientific work above related, the Governments of Singapore and of the Federated Malay States interdicted the use of polished rice in their institutions—hospitals, schools, asylums and gaols—with the result that beriberi is now a rarity.

We are now in a position to gather up the threads and sum up the evidence on which we rely for believing that beriberi is due to deficiency of vitamin. The points have been ably marshalled by Colonel E. B. Vedder of the United States Army Medical Corps, and the following is taken largely from his summary. The evidence is partly epidemiological and partly experimental. The former is very strong alone, but when supported by the latter the case is overwhelming. Thus, in institutions where decorticated or polished rice is used as the main article of diet for some time— three months or more consecutively—beriberi begins to show

itself, and when whole rice is substituted the disease disappears, and it is never seen among communities where undermilled rice only is used. A good example is the analysis by Vorderman of 279,623 prisoners in Java in 88 prisons ; in 51 of these polished rice was used and among the inmates of these 2·5 per cent. were attacked ; in 37 undermilled rice was used and only one case was seen among 10,000 inmates (0·001 per cent.). The latter form of rice was then adopted for use in all the prisons and cases no longer appeared.

Again, Tamils as a race eat only 'cured' rice, that is rice which has been parboiled before husking, by which means the husk is easily removed leaving the outer layers—the aleurone layer and germ—of the grain intact. The Chinese in Malaya, on the other hand, use decorticated rice. Beriberi is common among the latter, practically unknown among the former. It has been found that rice parboiled and then milled has considerably greater antineuritic value than milled rice without preliminary parboiling ; this implies that some of the vitamin has diffused into the endosperm. If the former is now soaked in water the vitamin diffuses out again into the surrounding water, as Aykroyd showed in 1932. In confirmation of this we have the fact that in British Guiana milled parboiled rice is used and beriberi does not occur.

One more example : Prior to 1910 native scouts in the Philippines used white decorticated rice and records show that out of a total of about 5000 there were some 500 cases of beriberi annually. The Board for the Study of Tropical Diseases in Manila having undertaken an investigation, from 1910 onwards undermilled rice was substituted for the decorticated and in the following years the numbers of cases were 50, 2, and 3 respectively, and further investigation showed that these scattered cases were among the few who had not eaten the undermilled rice provided.

Another instance of the benefits resulting from application of the knowledge acquired may be cited from the Philippines, namely at the Culion Leper Colony. This was opened in 1906 and beriberi was constantly present among the inmates and sometimes as large a proportion as one-third of the deaths occurring there were ascribed to it. Unpolished rice was then introduced and by 1910–11 there were no deaths recorded from beriberi and the total death rate had been reduced nearly 50 per cent.

As regards experimental evidence, this has been given in sufficient detail and calls for but passing mention, such as the human experiments of Fraser and Stanton on 300 Javanese

labourers whom they divided into two groups, feeding one on decorticated rice, the other on cured rice. Beriberi appeared in the former in three months. The conditions were then reversed and the disease appeared in the second group while ceasing in the first. The workers were allowed to mix freely with each other and the results rule out any idea of the disease being due to infection and contact. Strong and Crowell's studies among the prisoners at Bilibid, Manila, call for no further comment. The animal experiments with pigeons and fowls, performed by Eijkman from 1890 onwards, and later by Fraser, Stanton, Funk, Suzuki, Shimamura, Odake, Vedder and Williams, have been already summarized and further detail is of academic rather than of purely historical interest.

It is true that concentration on the character of the rice, at first as the chief and later, according to some writers, as the only source of beriberi has tended in the past to fog the issue somewhat. Wheat, corn, any suchlike grain when decorticated may be deprived of its vitamin by the process and the argument that beriberi is not due to the quality of the rice because it occurs in those whose diet is not mainly rice is not a valid objection—a diet of bread made of refined wheat- or corn-flour, macaroni, cornmeal, hominy, or of vegetable fats and oils, may each and all result in producing symptoms of beriberi. Hence, as Stanton noted long ago (see p. 881) a diet which appears to be well-balanced as regards proteid, fat and carbohydrate, and is of adequate calorie value, may nevertheless be deficient in antineuritic vitamins and be beriberi-producing.

Another objection which used to be raised, that if beriberi was a food deficiency disease it would be met with in times of starvation is also fallacious. It is not the sudden deprivation of food, but prolonged living on an inadequate diet (for example, those besieged in Kut), which ends in beriberi, for beriberi, as experimental investigation has shown, takes some three months to develop.

3. INFANT BERIBERI

Hitherto we have paid no attention either to infant beriberi or to what has been known as Ship beriberi, except incidentally when speaking of the disease arising where wheat-flour was used in place of rye for bread (p. 880).

As regards Infant beriberi : This has been a very potent cause of infant mortality in the past, particularly in the Philippines. Dr. Manuel Guerrero was the first to bring it prominently forward,

when he stated infant beriberi to be " a disease which constitutes a factor of the first order in the excessive infant mortality in these islands," but was " completely unknown in the annals of Tropical Pathology." It was generally considered by the local practitioners to be infantile eclampsia or convulsions due to epilepsy or to " nervous exhaustion resulting from gastralgia or colic." He indicated that several conditions passing under the local names of *taon*, *taul* and *suba* were all beriberi. From 1905–09 19,606 children died under twelve months of age, and 1461 from beriberi ; further nearly half (41·9 per cent.) of cases of convulsions he concluded to be cases of beriberi. Even as late as 1926 it was held by the Committee appointed that year to study the problem to cause over 16,000 deaths annually and 28 per cent. of all deaths under one year, and the majority were breast-fed infants. It was the general belief that these were children of mothers afflicted with beriberi, but in one-fourth no sign of this disease was found in the mothers. The condition resembles the wet form of adult beriberi but, unless we regard the aphonia, which is a characteristic symptom, as due to laryngeal paralysis, there is no indication of neuritis. A bacterial cause has been assigned to this, as in former days to adult beriberi. J. E. Montes found *Bacillus mycoides* or *B. mesentericus* in the bodies of infants dead of the disease, and claimed further that he was able to produce a similar condition in monkeys by its means.

Another place where infant beriberi was of importance clinically has historical interest because it affords also an example of a measure undertaken by a government with the object of benefiting the natives which nonetheless in the end did more harm than good. In Nauru (Pleasant Island) in the Pacific the chief article of diet is not rice but fish and coco-nut products and a fermented drink, toddy, made from the coco-nut palm. After the peace of 1918 the island came under Mandate of the Commonwealth of Australia and the making of toddy was prohibited. At the same time the natives used greater quantities of imported foods, white flour, tinned meats, refined sugar, etc. Infant beriberi increased and became a serious problem which was solved by the use of a toddy yeast.

In 1921 there was introduced in Manila an extract of the polishings from white, not red, rice ; it was known as *tiqui-tiqui*. It was prepared by extracting one part of the polishings in two parts of 25 per cent. alcohol for forty-eight hours, decanting off the fluid and pressing the residue, evaporating it in a distillation plant under pressure and at a temperature not above 75° C. The

syrupy product after further treatment with alcohol, centrifuging and concentrating, was standardized so that 1 mil of the extract was equivalent to 20 grammes of the original polishings, and it was given in doses of 3 c.c. every hour with most gratifying results. After its introduction and distribution to the poor admissions for infant beriberi in Manila, which in 1915 were 7·79 per cent. fell to 0·45 per cent. in 1927. Equally good success was reported from its use elsewhere.

4. Ship Beriberi

A few words may be added to the reference made incidentally (see p. 880) with regard to ship beriberi. The fact that the disease occurred on board vessels where rice was not used, at all events was not a staple food, was urged as an argument against the rice theory. The fallacy of this has been pointed out and need not occupy us further. Ship beriberi certainly differed from the usual types of the disease as seen on land and investigation has shown that it occupies a place intermediate, as it were, between, or is a mingling of, true beriberi and scurvy (see Darling's diagram, p. 880). The development of symptoms, in cases reported in the British Navy at least, is very slow, consumption of rice is certainly not a factor and the evidence of peripheral neuritis not convincing. In Norwegian ships the prevalence increased when the pea ration was reduced and tinned foods substituted for salt meat and, as has been already noted, when biscuit from rye flour was replaced by white wheat flour and bread made with it. T. H. Haynes remarked on its occurrence in the Australian Pearling Fleet after the men had been several months on board and he found that the use of wheat flour, beans, potatoes, etc., and exclusion of rice (that is, abundant vitamins) " mitigates, if it does not prevent, the disease."

5. Recent Work and Conclusions

When reviewing the state of our knowledge to-day and comparing it with that at the close of last century we must confess that in spite of all the research that has been carried out on vitamins the progress has on the whole been slow. Year after year the geographical range of the disease was shown to be more and more extensive than had been supposed. It was found to exist among the cassava (manioc) eaters of the Congo, among the natives of Madagascar, in Brazil where rice, maize and manioc enter largely into the dietary, in Cuba and Porto Rico, even in Spain where F. Martinez reported a case in Alpujaras, and this was probably

not the only one ; all this in addition to the previously recognized endemic centres—India, Ceylon, Malaya, the Philippines and the Dutch East Indies.

We learned not a little about the disease from experiences in the Great War. Thus, in the Dardanelles and Mesopotamia in 1916 beriberi occurred among the British troops whose diet was largely composed of biscuit, white bread, tinned and preserved foods. Privation and malaria were probably predisposing causes and all cases were of the ' wet ' type. The Indian troops whose diet comprised atta, a coarsely ground whole wheat flour, and dhal, dry pulses rich in antineuritic vitamin, escaped. Later, when horseflesh and brown bread made half of white flour and half of atta, were issued, the incidence fell. In Mesopotamia cases occurred also among the Chinese and the ships' crews of Indians.

Again, in Southern France cases developed among Indo-Chinese labourers and the Chinese and Africans, although after landing they had a good diet. It was thought that either the condition was developing during the voyage or that it was as it were latent and declared itself under changed conditions of work and lowered resistance following an influenza outbreak. There was no extension from sick to healthy and the supposed epidemics recorded in France by Chantemesse and Raymond resembled scurvy rather than beriberi.

Studies by Kimura, Honda, Ohida, Muira and others regarding the pathology of beriberi have demonstrated the degenerative as opposed to the inflammatory characters of the nerve lesions, evidence tending to favour the secondary results of toxic action ; nevertheless, none of the search for a toxin has succeeded in isolating it and the weight of evidence is all against the disease being of infective nature. We know that deficiency of the antineuritic vitamin is an essential (if we can logically say that the ' absence ' of something can cause something else—not an easy concept), but the manner of its action is still under debate. F. M. R. Walshe believed that defective carbohydrate metabolism resulting from the avitaminosis led to the production of a toxic by-product —a *positive* factor—an enzyme perhaps, which attacked the nervous system, thus helping to reconcile the food deficiency and the toxin theories.

McCarrison in 1919 was led by his experiments on birds and monkeys to the opinion that lack of vitamins in association with a starchy diet brought about dysfunction of the whole endocrine system, with resultant disturbance of carbohydrate metabolism

and assimilation, and muscular wasting. Disorder of the digestive system as a whole was brought about by an unnatural diet, facilitating invasion of the digestive tract by bacteria; in other words, an infective factor as well as the essential dietetic factor played a part. It may be so, but the sequence is unconvincing without more positive evidence.

There are many men of note who favour the *intoxication* theory. Thus, Ogata, Suzuki, Kagoshima, Oka and other Japanese workers in particular maintain, as others have done, that avian polyneuritis is different from human beriberi. They reported in 1923 finding a decrease of Vitamin B in the tissues of polyneuritic birds, but not in those of human cases of beriberi; also that anæmia develops in the former, not in the latter, and they suggest an intestinal intoxication, as did Hamilton Wright long ago in Malaya. Nagayo also in 1923 noted that the dilatation of the heart and hypertrophy of adrenals which were observed in human beriberi were not seen in avian cases and concluded that there must be some additional factor.

J. W. D. Megaw agrees that avian polyneuritis is different from human beriberi and that the vitamin deficiency acts merely as a predisposing factor, and that the exciting cause is consumption of damaged rice, toxins developing when it is stored in the hot, rainy season, thus reverting to Braddon's theory of a quarter of a century earlier. He states that the incubation period is too brief to be accounted for by deficiency—Stanton's experiments showed the usual period to be three months—and the comparative freedom of Calcutta from the disease since the erection of rice-mills he ascribes to the rice being stored as undecorticated paddy and sent out as freshly prepared polished rice, thus obviating need for prolonged storage.

It will not be considered redundant to repeat once again that we must not, when paying attention to rice as a causative factor, forget other factors which may be subsidiary or predisposing, for in countries where beriberi is common the diet of the people is often ill-balanced, and we find other diseases present which are also attributable to dietetic errors, in quantity, in quality, or in imbalance, for example pellagra, A and B avitaminosis, retrobulbar neuritis of Nigeria, Kwashiorkor on the Gold Coast, ' Central neuritis ' or Scott's palsy in Jamaica, and others.

Jansen and Donath (1927), J. L. Rosedale (1927), Williams, Waterman, Gurin, Peters and others within the past decade have believed that another factor is also at work, other, that is, than deficiency of Vitamin B_1 and they attribute the variability of

symptoms to the multiplicity of deficiencies, changes being ascribable to the relative degree of one or other deficiency or combination of them. Nonetheless, there is no disputing the established fact that the substitution of undermilled for milled rice has caused beriberi to disappear in one locality after another ; also that infant beriberi clears up when rice-polishings in the form of tiqui-tiqui are given. In the case of adults the evidence is not so clear, because it is rare, if ever, that Vitamin B_1 is given alone ; other dietary changes are made at the same time as part of the treatment.

Further evidence that vitamin deficiency is not the sole factor can be furnished by epidemiological investigations. In India, for example, rice-eating is general, but beriberi has more or less its endemicity, as in Madras. In certain areas strict rice-eating Hindus suffer less than other classes which do not so limit their food ; also in these areas beriberi is seen among millet-eaters. Though the diet is the same in all the gaols in Madras, only those in certain endemic areas are attacked. It would seem inevitable to infer that there is some factor additional to the intrinsic nutritional one. We can speculate even further regarding this ' intrinsic ' factor for rice found to be relatively less deficient in Vitamin B appears to be more liable to bring about the condition than rice relatively more deficient. As Graham has put it : Supposing 100 equals the amount of vitamin necessary to keep pigeons in health, 70–90 will be followed by beriberi, 50 or less by polyneuritis ; in other words true beriberi is due to insufficiency rather than to absence of the factor. This has been dealt with already when we spoke of the distinction between polyneuritis and beriberi in birds and of McCarrison's researches.

In 1928 Mebius and Wenckebach brought forward their " water-retention " theory. They showed that œdema occurs in the heart muscle, chiefly intracellular, in wet beriberi ; that excess of water interferes with the normal fluid exchange and so with contractility. Control of osmotic pressure, they affirm, depends on the presence of Vitamin B and all the other symptoms are explicable by water-retention.

Evidence furnished by increase of the disease which has been recorded in various parts of the Far East during the past twenty years has also much weight. A few such may be mentioned : Thus Cazenove has recorded that in 1916 there were in Cochin China 988 admissions on account of beriberi and 197 deaths. The next decade was a time of prosperity for the natives and they were able to afford a " better quality of rice " and in fact substituted

polished rice for the coarser product to which they were accustomed; in 1928 admissions for beriberi numbered 3245 and deaths 600.

Japan affords another example : Fukushima reports that in 1912 the incidence of beriberi in the Japanese Navy was 1 per mille ; in 1919–21 it rose to over four, and the fourfold increase was ascribed to more extensive use of a white rice ration. That this was probably correct was shown by the benefits resulting when this was again reduced. An even more striking instance is afforded by Lichtenstein's records of cases in the Dutch East Indian Army. In 1918 the incidence was only 1·8 per thousand ; in the following year the issue of unpolished rice was stopped and in the first eight months of 1922 the rate of incidence had risen to more than fourteen times as great, namely to twenty-six per thousand.

In places where beriberi is endemic, observation and analysis show that many of those not actually presenting symptoms of the disease are living, as it were, on the verge of nutritional disturbance—in short, in a ' pre-beriberi ' state. More attention needs to be paid to this. Where the diet is ill-balanced, other adverse conditions—climatic, excessive heat, humidity, lack of exercise, or fatigue from over-exertion, illness of one kind or another—may weigh down the scale and cause beriberi to develop without change in diet.

The subject is by no means cleared up yet. Cases are described under the term *enterogenic beriberi* in which the diet cannot be said to be deficient in Vitamin B_1. The symptoms are diarrhœa, polyneuritis, œdema, some cardiac disturbance, hyperæsthesia of the feet, but the tendon reflexes may not be abolished. An explanation put forward is that, owing to abnormal conditions in the alimentary tract, absorption is defective though the vitamin content of the food is adequate. Improvement, even complete recovery, may occur if the gastro-intestinal condition is treated, though little change is made in the character of the food.

B. EPIDEMIC DROPSY

1. EARLY VIEWS

Epidemic dropsy is of interest because in the fifty odd years since attention was first called to it by Colonel Kenneth McLeod in Calcutta there has been much discussion and no little investigation as regards its nature and causation, all within a comparatively

limited range, yet even now it cannot be said that its ætiology is clear.

McLeod in the *Indian Medical Gazette* gave a description in 1881 of an outbreak of disease in Calcutta which he regarded as having certain affinity with, but at the same time as being distinct from, beriberi, chiefly because of the presence of fever and a rash, of the absence of peripheral neuritis, or at least of there being less evidence of it, and, as he thought, of its communicability. *He had observed it in Calcutta and in Howrah, a suburb of Calcutta,* occurring in epidemic form in each of the four preceding years, 1877–80. Record had been made of its occurrence in Assam and other parts of India and in Mauritius in 1878–9, after the introduction of coolies from Calcutta where an outbreak was in progress. In 1876 there had been a famine in India and many cases of dropsy had been observed which had been considered to be beriberi, but they diminished in number, in fact almost disappeared, in the hot season, reappearing annually till 1881. The outbreak in Mauritius was also regarded as beriberi by Fayrer, for both in India and Mauritius, although the patients exhibited no marked paralysis nor sensory changes, those attacked were subsisting on a poor diet the chief articles of which were decorticated rice and dhal (legumes of the Phaseolus genus).

McLeod, after observing the 1877 outbreak in the rainy season in Calcutta and its southern suburbs, and the following year another in the villages east of the town and a recurrence again *in 1879, described it as a " new disease,"* though he was cautious to add that it might have occurred before and its epidemic character had now brought it into prominence, or that it had been confused with other conditions of which dropsy was a marked symptom, such as *Chiao-ch'i* mentioned by Hwangti, it is said, in China in 2687 B.C., and described in Ch'ao's pathology in A.D. 610, and the condition referred to by Bontius in 1642 and Malcolmson in 1835.

Simultaneously with McLeod's " new disease " another was being noted by Japanese observers, under the term *kak'ke;* this is now considered a synonym of beriberi, but the condition when first described in 1880 was thought, on account of the acuteness of onset and course and by its general characters, to differ from true beriberi; others were of opinion that it was an acute and perhaps aberrant form of *Shoshin* (beriberi), aberrant in that no paralysis or neuritis was seen, but only œdema, diarrhœa, dyspnœa and cardiac weakness.

Again, between 1875 and 1880 outbreaks of a disease similar

to this had been observed in the prison at Singapore and had been denominated by Irvine Rowell as " beriberi unconnected with diet."

The symptoms of this " new disease " may be stated briefly, for it was on these that ideas were based by those supporting and those averse to the view that it was a form of beriberi. These symptoms were rise of temperature, soon followed by dropsical swelling starting in the feet and extending up, even to the face ; pleural and pericardial effusions were not uncommon, but ascites was rarer ; there were burning and pricking sensations in the skin but no numbness or paralysis. Dyspnœa, palpitation and rapid pulse and, later, enlargement of the liver (secondary perhaps to the cardiac dilatation and back pressure). The average length of illness was six weeks, but it might drag on for two to three months, or terminate fatally in a week. Some patients—and those in Mauritius seemed to show this more than had those in Calcutta—had suffered from vomiting and diarrhœa at the onset and others exhibited cutaneous eruptions. The fatality rate was 2–3 per cent. in Mauritius, three or four times as high (8–10 per cent.) in Calcutta.

Nomenclature of the Condition

We have seen that in the early days of this disease, as described by McLeod, it was known as the New Disease, or the New Indian Disease. In 1879 Payne named it ' acute œdema ' and O'Brien ' acute dropsy ' from its most striking symptom. Others at the same period, namely Cayley in 1878 and Chambers in 1880, called it ' epidemic fever '—a poor effort applicable to any of the exanthemata or to influenza, and quite indistinctive and non-committal. At a meeting of the Calcutta Medical Society (perhaps its first meeting) in 1880 Smith stated that it was known to some as ' lymphatic fever ' because the œdema was thought to be due to blocking of lymphatics. Ray, who saw an extensive outbreak in Madras, spoke of it as ' Madras beriberi ' and affirmed that the Calcutta disease was the same, thus opening up the question whether the Madras outbreak was epidemic dropsy or the Calcutta outbreak beriberi. Sir Joseph Fayrer gave as his decided opinion that it was beriberi, while J. N. Coates, an equally good authority, as strongly maintained the opposite. McLeod in 1881 and, some sixteen or seventeen years later, Sir Pardey Lukis considered it as quite distinct from beriberi, and in 1908 a special meeting of the Asiatic Society of Bengal was held to debate the question and the upshot was to sustain the opinions of McLeod and Lukis.

Mauritian doctors called it ' acute anæmic dropsy ' or, according to one authority, Dr. Clarenc, ' hydropie scorbutique aigue.' There were others who advocated for its connection with scurvy, for example Madras physicians who, seeing an outbreak after a time of famine, spoke of it as " a nutritional disorder with hæmorrhages." Greig in 1911 associated it with ship beriberi, but thought it different in many respects from the beriberi occurring among the Chinese in India. Braddon, a man of note in the beriberi investigation (see p. 883), thought, with Greig, that, since in ship beriberi there was marked dropsy, especially of the legs, with weakness and dyspnœa, cardiac distress but no neuritis, and since, in his view, true beriberi and ship beriberi strongly resembled one another, therefore ship beriberi and epidemic dropsy ought to be regarded as one.

Owing to the cutaneous eruptions which might accompany it, no less an authority than Dr. Chevers, in a paper read before the Medical Society of London in 1884, proposed the name *Febris exanthematosa orientalis*, which, of course, would be applicable to half a dozen diseases. Others, yet again, believed that pure beriberi, as seen at Singapore, epidemic dropsy as seen in Calcutta, and the contagious exanthem of Mauritius were but three phases of one disease. Sir Pardey Lukis who saw many cases of beriberi and of epidemic dropsy stated : " In the majority of cases of epidemic dropsy very distinct skin lesions are present, especially in the early stages, and give the impression of an exanthematous fever." He gave it yet another name, ' angiomatic œdema,' and considered it to be allied to urticaria and erythema nodosum, and further that some kind of intestinal sepsis (a better term than its substitute in more recent times, ' auto-intoxication ') led to serum infiltration, and this association of eruption, dropsy and gastro-intestinal disturbance led to the diagnosis of cases in Benghazi, Northern Africa, as *exanthematous hydropic gastro-enteritis*. From 1907 onwards the beriberi theory gained ground—the evidence for and against will be mentioned later—and Megaw, Greig, Acton, Chopra and others regarded it as the ' epidemic dropsy form of beriberi.' Pearse in 1908 concluded that it was beriberi, but in 1912 Greig on further consideration was convinced that it was a deficiency disease but that there were no adequate grounds for regarding it as either infectious or really ' epidemic.'

It must be confessed that the name ' epidemic dropsy ' is not altogether satisfactory ; the disease may remain endemic and by no means always occurs in epidemics ; moreover, the dropsy may not appear till fairly late, and there are other forms of dropsy

which are more often epidemic, as war œdema, famine œdema and wet beriberi ; lastly the name pays no regard to the presence of an eruption. In 1932 J. C. Mukherji proposed yet another name, ' hæmangiectatic œdema.' It would be well, however, not to multiply synonyms but rather to wait until its ætiology has been elucidated and its nature more accurately determined ; until then ' epidemic dropsy,' the term assigned by its first describer, Colonel McLeod, is quite a convenient label.

Before passing to an enumeration of recorded outbreaks in their chronological order we may make a few remarks on outbreaks in general. The condition is not confined to India and the East ; in fact, some maintain that it occurs in temperate climates also and quote an outbreak from 1894–7 in the Richmond Asylum, Dublin, and another in the following year in France at the St. Gemmesey-Loire Asylum. That these were the same condition is very doubtful ; in fact, in the light of recent study we can affirm almost definitely that they were not. Outbreaks have, however, been reported in Sierra Leone, Benghazi, Mauritius and Réunion, though they were usually regarded as beriberi.

S. C. Seal and M. N. De, who have done more than any to trace the earliest accounts, are of opinion that Waddel's description of an epidemic in Rangoon over a century ago (in 1827), characterized by œdema of the legs, hæmorrhage from the gums and the bowel, with diarrhœa, anasarca, and a high mortality among the Indian troops after they had occupied the town in 1826, was epidemic dropsy, but the symptoms might equally well be explained as scurvy. Again, it is the opinion of some that the ' prison dropsy ' reported during the decade 1847–57 in Europe and America also was epidemic dropsy, on the grounds, open to fallacy, that ' Asiatic beriberi ' in Indian prisons in more recent times was the same condition. [We must bear in mind that there are authorities of repute at the present day who maintain that epidemic dropsy so-called and beriberi itself are but different manifestations of the same disease.] It is curious, however, that neither in the Calcutta outbreaks described by McLeod nor in those of œdema in the Madras Presidency shortly before, following a famine, was a single instance of neuritis recorded. It may be that the half-starved arrivals from Madras brought the disease to Calcutta, for it started in the latter where passengers from Madras would land and stay for a time. It is a difficult question, for all the weight of evidence subsequently acquired is against infection.

If we accept the statements of the writers of the last quarter of the nineteenth century, and though we must do so with reserve

we have no means of checking these statements, we are driven to conclude that the ' new disease ' had probably existed in Africa, in Japan, in China, Malaya, the Straits Settlements, Burma and Southern India before it was recognized and reported by McLeod in Calcutta, and within the ensuing two years was recorded also in Dacca by Crombie, in Shillong, Cachar, Khasia Hills, Assam by O'Brien, in Sylhet by Nairne, and Bengal by McConnell, all in 1879, and in Allahabad by Deakin, and in Mauritius by Lovell in 1880.

The ' dropsical disease ' of Haiti has been thought to have been another instance of this condition away from the East, but there can be little doubt that the œdema here was due to ankylostomiasis which is common in the West Indies but had not been heard of at that time.

The following is a list of such outbreaks of epidemic dropsy as we have been able to find recorded since the beginning of the present century :

1901   Cases again seen in Calcutta, there having been no record of any during the preceding twenty years.   Cases were admitted also into the General Hospital, Madras.
1902   Small outbreak in Bombay.
1903   Outbreak in Barisal Gaol.
1905   Outbreak among those living in the Garo Hills.
1907   Outbreak in Basti Gaol (Greig).   Also in Darjeeling (Pal).   In Calcutta, and it was noticed that some of the patients suffered from peripheral neuritis.
1908   Outbreaks at : Alipur Reformatory School (Pearse), in Darjeeling (Munro), Dacca (N. Campbell), Mymensing (Rutherford and Delany), Chittagong (Delany), Sylhet (Delany).
1909   More severe outbreak in Calcutta, many cases fatal ; it is said that 433 died from it, 336 Hindus and 97 Mohammedans.   Also in Sylhet, Assam.
1919   Again in Calcutta ; 96 deaths recorded, of which Hindus constituted three-fourths, Mohammedans only one-fourth ; four times as many females were affected as males.
1920   In Maldah Gaol.
1923   In Allahabad (reported by Megaw and Banerji).
1924   Rangoon and also Calcutta (Megaw and Bhattacharjee).
1924–6   Surada in the Ganjam district, Madras.
1926–7   The worst epidemic that had visited Calcutta till then ; the fatality rate was high.   In 1926 there were 939 deaths and in the succeeding year 630.   At the lowest estimate cases numbered ten times this.   The disease extended to adjacent districts.   In this epidemic cutaneous eruptions were more in evidence ; it was noted that the flexor surfaces were more often involved, but the rash might be generalized and was accompanied by sensations of burning and itching, *especially*

of the legs.   Some patients suffered from hæmorrhages—from the gums, the lungs, the stomach and the bowel.

The same year another outbreak occurred in Fiji, beginning in November and extending into 1927.   It was restricted to the Indian population, but broke out in every Indian settlement in the Colony.   There were 33 admitted to the Colonial War Memorial Hospital and three died, and to other hospitals 37, one of whom died.   It was remarked that multiple retinal hæmorrhages were common, and others showed neuro-retinitis, or optic neuritis without hæmorrhages.   This outbreak helped considerably to elucidate the cause of the condition and is referred to again in the section dealing with the ætiology.

1928   Allahabad ; Birbhum ; Burma.   Over 100 cases occurred at Birbhum.   This is referred to again later as investigations in connection therewith had important bearing on the problem of causation.

Subsequent to this the disease appeared farther west, in Bihar and the United Provinces, where Seal and De carried out some intensive investigations from which much important information was obtained.

Outbreak occurred in Sierra Leone (Burnett).

1935   Explosive outbreak in Benares.   Also in Rangoon.   The disease was made notifiable and subsequent to this 429 cases were reported.   The disease appeared first in the cities and towns and later in the villages in the neighbourhood.

The question of confusion with famine dropsy calls for only passing mention.   The ' prison dropsy ' reported in Europe and America in 1847 has been referred to above.   Morse's account of the outbreak among the Boer prisoners of war in St. Helena in 1902–03 is instructive.   The insanitary habits of the prisoners were held to be the cause—vitamins had not then been heard of —and it was vaguely believed that beriberi had been brought in by some of the Boers and had then spread by reason of their habits. There were no cases among the British troops although their food was said to be ' practically the same.'   The clinical features of special note were great swelling and œdema of the legs and scrotum which might appear quite suddenly and disappear as quickly and, if ataxia were present, it, too, rapidly cleared.   The nature of the ataxia is not specified ; if it was neuritic the condition was more like beriberi than epidemic dropsy.   Œdema was seen also in prisoners of war in Germany and Russia where the diet was deficient or ill-balanced and consisted chiefly of bread.   Attention may be drawn to the fact that as long ago as 1864 Cornish in Madras had written pointing out the distinctions between ' famine dropsy ' or ' war œdema ' and beriberi.

Before we consider the work that has been done to discover the actual cause of epidemic dropsy it will be well to clear the

ground by pointing out the similarities to and differences from beriberi as usually described. As regards the former : the disease occurs .among those whose staple food is rice ; the seasonal and age distribution are the same, if we except infant beriberi ; it is prone to occur in institutions ; dropsy and cardiac disturbances are common to epidemic dropsy and the wet form of beriberi. On the other hand the differences are marked : Thus, epidemic dropsy attacks chiefly those who eat parboiled rice, whereas beriberi attacks those living on overmilled rice ; fever is common (some Japanese observers state that fever is present in the early stages of beriberi, but this is not the general opinion) ; gastrointestinal disturbance is common and certainly more marked a feature of epidemic dropsy ; signs of peripheral neuritis are lacking (it is said that the knee-jerks are diminished or lost in a varying proportion, 20–60 per cent., but in some cases they are exaggerated throughout the illness) ; glaucoma is a common complication or sequela, not found in beriberi though some patients suffer from dimness of vision and ' scintillation.' A hæmorrhagic tendency is present in some outbreaks of epidemic dropsy ; it is not seen in beriberi.

To sum up : The absence of cases among infants and of the characteristic peripheral neuritis (this was noticed in one outbreak in Calcutta, but in this there may have been a mingling of the two diseases), the presence of fever, of gastro-intestinal disturbances, of roseolar or petechial or verrucoid eruption, telangiectases, bleeding from mucous surfaces and the development of glaucoma, seem sufficient to warrant epidemic dropsy being clinically distinct from beriberi.

2. ÆTIOLOGY

Theories which have been brought forward to account for this condition may be grouped under four heads : (*i*) That it is due to avitaminosis, or (*ii*) Rice. (*iii*) That it is a contact infection. (*iv*) That it is caused by a toxin.

1. *Avitaminosis.*

The idea arose in the similarity between cases of epidemic dropsy and wet beriberi, but what appears to be an insuperable objection is the rapidity of onset together with the fact that at times the diet is varied and not deficient in vitamins. Thus in 1923 Megaw and Bauer described two family outbreaks in India. In one twelve out of thirteen members of a family were attacked, the symptoms being typical, and two died ; also a relative coming

on a visit was attacked within three days of arrival—clearly too soon for avitaminosis, even had the diet been deficient, which it was not.

The second outbreak was similar but of milder type. It is to be noted, however, that no more cases occurred when the rice was omitted from the diet. Hingston also, three years later, when investigating outbreaks in Bengal, pointed out that no vitamin deficiency was to be found. It had been noted, though the point is not of major importance either way, that outbreaks might rise and fall with the price of grain foods, so that the poorer natives could not afford to supplement the rice with other, protective, articles. Against this must be set the fact that epidemic dropsy does not always attack the poorer class of native.

2. *That it is due to Rice.*

Evidence brought forward in support of this included the following points : (*i*) The disease seemed to be confined to rice-eaters and usually those who used parboiled rice ; (*ii*) Bengal rice was incriminated in particular, because the disease was common in Calcutta and its neighbourhood, or in places whither Bengal rice was sent ; (*iii*) The reason given for cultivators in Bengal not being attacked was that they probably would store it as *padi* and prepare small quantities of it at a time as required, while institutions and labour forces were the greater sufferers because they had to live on rice stored after treatment ; (*iv*) Explosive outbreaks might arise among those whose only change in diet compared with that of their associates was that they obtained their rice from a different source. Thus, Howrah notes in 1926 that 250 persons were living under similar conditions and on the same diet, but 100 of them obtained their rice from one particular shop. Of these there were ninety-six attacked during the ensuing twelve days, whereas none of the 150 who bought theirs elsewhere suffered. (*v*) That outbreaks were most likely to occur at the end of the rainy season when the rice eaten had been stored during the hot damp weather.

The investigations, field studies and experimental work carried out by the staff of the Institute of Hygiene and Public Health, Calcutta, in that city and in Bihar, Orissa and Assam, have thrown much light on the subject in recent years and their reports form some of our most reliable and instructive sources of present-day knowledge. In discussing Acton and Chopra's rice theory of epidemic dropsy the report states : Certain varieties of rice stored under certain conditions of temperature and moisture become

infected with organisms of the *B. vulgatus* group which produce a toxin soluble in water, this toxin being the cause of the disease. Parboiling kills the enzyme, and milling or polishing, by injuring the grain, assists invasion by the organism, producing opacity in the grain. Against this the epidemiological evidence is strong. Only the poor people keep and drink this rice-water ; other classes throw it away, yet the incidence of epidemic dropsy is lowest in these poorest classes as shown in the table reproduced below :

Status.	Number.	Affected.	Unaffected.	Percentage affected.
Very poor	69	0	69	0·0
Poor	662	9	653	1·4
Lower middle . . .	530	30	500	5·7
Middle	138	21	117	15·2
Upper middle . . .	51	2	49	3·9
Rich	11	0	11	0·0

From the bacteriological side there is no proof that the natural opacity of rice grain is due to these organisms. " Wholly chalky kernels .˙. . sometimes occur in crops of otherwise fine rice," says Copeland. Further, attempts were made to produce opacities in the clear grain by storage under certain conditions of temperature and humidity after inoculating them with ' rice bacilli,' but unsuccessfully. On the other hand, samples of rice were obtained from various districts in the Madras Presidency where there was no epidemic dropsy. Some of these contained a large proportion of opaque grains, but attempts to cultivate sporing aerobic organisms from them were fruitless.

3. *Contagion.*

In an outbreak at Kulna (recorded in the *Indian Medical Gazette*, 1927) there seemed to be some indication of person to person infection, but there is much left to explain even then, such as what is the causal agent, what is its nature, what are its portals of entry, how is it transmitted ? Moreover, seeming contact may find a more ready explanation in community of origin, as when several members of a family are attacked, though all may not succumb at the same moment. On the other hand there are still more instances in which those in closest contact with cases of the disease escape attack, and introduction of patients even in an advanced stage into an unaffected family does not result in secondary cases. In fact congestion in houses was found to be ' negatively correlated ' with incidence of the disease (due regard

having been paid to the population at risk).   This factor probably linked up with economic status (R. B. Lal and S. C. Roy).   To test the theory further, patients about a week after the onset of symptoms were made to sleep, under controlled conditions, close to healthy persons.   None of the latter contracted the disease.

4. Toxin.

This question resolves itself into two parts : (a) The vague notion of some toxin, bacterial or other, developing in the rice eaten, and (b) a more specific incrimination of a certain poison, a toxic adjunct to the rice, to wit mustard oil.

(a) The former of these has been dealt with to some extent under (2) above, when discussing the theory that the cause was rice, apart from mere vitamin deficiency.   The general view was that the rice had been stored under faulty conditions, usually of temperature and moisture, whereby certain organisms present, saprophytic in nature, developed and multiplied and became pathogenic or produced a nocuous toxin, and the difficulty was often taken as solved when the conclusion was stated that the disease was due to " some toxin developing in rice stored under unsatisfactory conditions."   This seemed to find support when the diet was examined and found not to be deficient in vitamin ; further, the use of rice as the staple food of patients could be excluded in rare instances only, but rice was also the chief food of those who did not suffer.   Although the toxin was held to be water-soluble, the habit of discarding the rice-water, as we have seen above, furnished no protection against the disease ; on the contrary more cases occurred among the classes who threw away the rice-water.   Analysis of cases showed that those whose custom it was to use sun-dried and hand-pounded rice might suffer equally with those taking parboiled and milled rice.   The question of toxicity of opaque grains and the action of bacteria in causing the opacity was, by the studies of Lal and Roy, ruled out as baseless. Members of the *Bacillus vulgatus* group, especially in a medium-grade rice known as ' balam,' were at one time incriminated, their action being intensified by destruction of protective enzymes brought about by the mode of preparing the rice.

(b) Toxic admixture with the food, usually rice.   Mustard oil appears to have come under suspicion first when an outbreak of epidemic dropsy was investigated in Fiji in 1926–7.   At the Colonial War Memorial Hospital thirty-three patients were admitted and three of them died ; at other hospitals in Fiji there were together thirty-seven admissions and one death, and ' several

hundred' mild cases received out-patient treatment. Cases occurred in practically every Indian settlement in the Colony, and suspicion was drawn to some article of food used by Indians but not by others, as the disease was confined to the former. Mustard oil was suspected and analyses were made of it not only in Fiji but in England also. The solution on this occasion was somewhat dramatic. At the Suva Gaol the rations distributed to each man were known. Except for extras ordered by the medical officer for special inmates, or patients, the only persons having extras were members of the cooks' mess who received an extra pot of curried vegetables and an additional ration of mustard oil; of this the prisoners received three-fourths of an ounce and the cooks' mess 1½ oz. per man. Three members of the mess developed the symptoms of epidemic dropsy in rapid succession. No cases occurred among the prisoners and no more among the cooks' mess when mustard oil was withdrawn and coco-nut oil and Colman's mustard substituted. Deva Sagayam of Nadi who investigated the cases noted the unusual feature of peculiar cauliflower-like, hæmorrhagic sarcoids, pedunculated, varying in size from that of a pea to that of a walnut, bleeding readily and profusely. They had been noted previously in cases in Calcutta.

In the last quarter of 1928 an outbreak occurred in Birbhum, Bengal, over 100 persons being attacked, and this was traced to a special consignment of mustard oil, but not definitely proved to be due to the oil—rather to some adulterant. The owner of the oil mill concerned had, a few months previously, received some wagon-loads of a seed resembling *pakra* seeds; a seed resembling mustard seed is common in the district and it and the local *kaur* thorn seed are often mixed with the genuine seed.

In 1930 Kanagarayer gave details of three cases seen by him at Ipoh, Perak, Federated Malay States. The patients were two Bengalis, husband and wife, and their Tamil cook. After a meal containing a certain mustard oil they were all seized with epigastric pain and nausea, succeeded by œdema of legs and feet, with large erythematous patches on the legs and circumscribed ecchymoses on the trunk. Inquiry failed to incriminate any article of diet other than the mustard oil which might have deteriorated from long storage or have been subjected to adulteration.

On the other side, cases have been reported from a gaol in Upper Burma, in 1927, where mustard oil was said not to be used and, further, in Calcutta cases occur among the Makwaris who never take it.

The evidence certainly is strong but not complete, and the

actual deleterious constituent is not known (for comparison, the reader is referred to the cases of Jamaica ginger paralysis, obscure at first, later proved to be due to an adulterant, see p. 951).   Many use the oil both as food and also externally in baths, and in South Calcutta investigation showed that cases of the disease occurred only among those who used it as food.   Thus, 160 cases were observed among 968 Bengalees (16·2 per cent.) taking it with food, but only one-fourth that proportion, 25 among 608 non-Bengalees (4·1 per cent.) who used it.   All the Bengalees consumed it, but of non-Bengalees 298 did not and there was no case in this group. The low incidence among the non-Bengalees who used it, as compared with that among the Bengalees, is not explicable at present, for in other respects their mode of living was the same. There is certainly a correspondence between the endemic area of the dropsy and the districts where mustard oil is habitually used, as Lal and Roy's investigations show, and in these areas the disease is limited to the users of it.   An outbreak at Jamshedpur in October 1936, and the research carried out in connection with and as a result of it are very instructive.

Jamshedpur is an industrial town of about 100,000 population, and prior to October no case had been seen there.   Then in the course of five weeks 222 cases occurred in sixty-six families ; 185 were in fifty-two Bengalee families and thirty-seven in fourteen non-Bengalee families who, however, had adopted Bengalee diet. The families attacked had all obtained the oil from the same source, or of the same brand, during October or the first week of November. Experiments were carried out on volunteers who for this purpose were divided into four groups : (*i*) Were fed on ' diseased ' rice and the suspected mustard oil, the food being cooked in the oil. (*ii*) Were fed on the same sort of rice but cooked in sound, gaol-produced mustard oil. (*iii*) Were given clear healthy rice and the suspected oil. (*iv*) The same rice and gaol-produced oil. Cases of the disease appeared in the first and third groups, that is, in those only who had partaken of the ' suspected ' mustard oil. The premonitory gastro-intestinal symptoms appeared in five days and the œdema and other symptoms between the ninth and twenty-third days.   Efforts to isolate the toxic constituent were not successful.

Another point, of secondary rather than primary importance, is worth noting in passing—the ages of those attacked.   Breast-fed infants escaped altogether (thus differing fundamentally from beriberi) ; cases were rare in those under five years of age, but after that the proportion was fairly high and maintained at an

almost constant level, indicating, if the mustard oil theory be correct, that the very young who do not take it are exempt, children who have very little are rarely attacked, while the adults and older children living on ' adult ' food suffer equally. The following table, issued in 1935 by the Institute of Hygiene and Public Health, Calcutta, makes this clear :

Age-groups in years	−½	½–1	1–3	3–5	5–15	15–25	25–35	35–45	45–55	55–65	65–
Incidence per cent.	0·0	0·0	0·7	3·4	27·6	25·2	24·1	23·8	24·8	23·3	21·6

As regards racial susceptibility the disease is almost confined to Asiatics and of these the Bengalees have up to the present been mainly affected, and it is to be noted that their diet differs from that of others in containing much rice and mustard oil. Next to the Bengalees come in order Annamese, Madrasis, Biharis and Oriyas. As regards religion and any connection between it and the disease the findings are too variable for it to be considered as of any weight. Thus, the incidence in Gourangdih (Bihar and Orissa) was high among the Mohammedans, some four times that among the Hindus, whereas in Karmigunj (Assam) no Mohammedan cases were seen, but 2·2 per cent. of the Hindus ; in another part of Assam more Mohammedans than Hindus suffered.

As a summary of the main features of this disease the findings of R. B. Lal and S. C. Roy of the Calcutta Institute, whose work has been mentioned in the foregoing, put the case very tersely and succinctly. Their observations were made as recently as 1937 and were based on a study of nearly 1000 cases in Assam, Bengal, Bihar and Orissa, in rural, semi-rural and industrial areas. Among their conclusions were the following :

1. The disease is almost exclusively confined to the Bengalees and those who have adopted their mode of life, especially with regard to their food habits.

2. The sexes are equally liable to suffer.

3. It claims its victims irrespective of religious grouping, depending upon local circumstances ; higher classes among the Hindus are the worst sufferers and the menial classes usually escape.

4. It is mainly a disease of middle-class people.

5. The age distribution is very striking ; babes at the breast do not suffer ; it is rare under three years of age, and very few are under five years ; above this there is not much difference.

6. Rice as the principal article of diet of the patients can rarely be excluded.

7. The habit of discarding water in which the rice has been boiled does not afford any protection ; hence the cause is not likely to be a water-soluble rice toxin.

8. There is no evidence that bad storage of rice is a factor, nor is there any clustering of cases around a common stock of rice.

9. No case was observed among those who did not use mustard oil in their food.

10. In the case of the Jamshedpur outbreak the evidence associating it with a particular brand of mustard oil was strong.

11. Cases develop more frequently among those who give a history of contact with patients, particularly family contact, than among those who do not, but this factor is usually linked up with community of food supply.

To these we may add, as Seal and De have pointed out, that

12. Epidemic dropsy differs from many other epidemics in that it is liable to affect groups of persons in limited areas, rather than large numbers nearly simultaneously.

13. It may prevail at high altitudes, or in the plains, in cold seasons or hot, and seems to have no relation to the rainfall.

C. PELLAGRA AND PELLAGROID CONDITIONS

If common report and popular belief were to be accepted as history Columbus would have many things to answer for besides the discovery of America, in particular the introduction of syphilis and pellagra.   It is with the second of these that we have now to concern ourselves.

Pellagra is by no means limited to warm climates but is met with so much more frequently in the tropics that it has come to be regarded as a disease of warm climates and, when encountered in temperate zones, to be considered as sufficiently rare as to merit recording.   The earliest accounts of the condition come from Continental writers, Spain being the first country where it appeared towards the end of the seventeenth century after the introduction of maize.   The significance of this will be seen later.   The first to give a recognizable description was Gaspar Casal of Oviedo who wrote of it in 1762, though he had observed cases for thirty years preceding, the disease being called *mal de rosa* by the Asturian peasants.   Thieri, a French physician who visited Spain, published in 1755 a report on these cases and Casal's observations.   In the same year, that is twenty-five years after Casal had seen cases in Spain but before his description was made public, Antonio Pujati saw it in the Province of Bellona, but did not, so far as we know, record his observations in writing, for the first Italian

account of it appears to have been that of Francisco Frapolli of Milan describing the disease in Lombardy, where it was known vulgarly as 'pellagra,' his work being entitled *Animadversiones in morbum vulgo pellagram*. By 1776 the disease was so serious in this country that a special inquiry was undertaken and, the disease being attributed to maize in certain conditions, the sale of unsound maize was prohibited. In 1784 a 'pellagrosorio,' or hospital for the treatment of these patients was established in Italy at Legnano and Gaetano Strambio was appointed in charge. Four years later this hospital was closed and Strambio was transferred to the Ospedale Maggiore, Milan. He published his observations in three volumes, and later, in 1794, summarized these in two *Dissertazioni*, at the same time discussing the writings of others. Twenty years later (in 1814) Guerreschi put forward the view that pellagra was a toxic condition resulting from the presence of moulds in the maize and pointed out as analogous the ergot (*Claviceps purpurea*) in rye. By 1818 it was known to be endemic in France, though it was not till 1829 that Gustave Hameau, of the Teste-de-Buch district, read a paper before the *Société Royale de Médecine de Bordeaux* relating its presence among the inhabitants to the south of the Bay of Arcachon. In 1839 it was known to be present in Corfu and it was later shown to have been endemic there since 1856; in Rumania it was known in 1846. By 1864 records of its presence in the United States were published, but it was not known to be an endemic disease there until Searcy reported an outbreak in Alabama in 1907. The following year Lavinder, of the United States Public Health Service, published a *précis* on the subject.

We need not trace its spread further, but its increasing prevalence in countries where it was already known is indicated by the fact that by 1830, in the Province of Lombardy, there were more than 20,000 cases among a population of a million and a half, and in some districts the incidence was as high as 3·5 per cent. Fifty years later there were over 100,000 cases, the population having by then increased to more than 16,000,000, and between 1870 and 1880 there were 100,000 cases in one year in Italy, and in 1872 Lombroso again affirmed that the use of maize was the cause. By 1918 there were 70,000 pellagrins in Rumania and between 30,000 and 50,000 among a population of 1,300,000 in Transcaucasia, females attacked being thrice as numerous as males. At the same time it was progressing in the United States; C. H. Lavinder estimated that between 1907 and 1912 there were 30,000 cases with a fatality rate of nearly one in three, and in 1916 there

were 150,000 cases in the Southern States with a 10 per cent. fatality rate. It seems strange to us how the disease came to be overlooked ; thus it was first recognized in Illinois State in 1909 ; nevertheless three years later 500 cases were recorded and many more probably were actually affected. The Thompson-McFadden Pellagra Commission in the United States made an intensive study of the disease in Spartanburg County, South Carolina, and found it rife among the mill-workers particularly. Those engaged only in household duties comprised nearly half (47 per cent.) of cases. The white population afforded approximately five times as many cases as the negroes.

The disease was not recognized in Great Britain till even later ; Cranston Low reported cases in Scotland in '1909 and Sambon and Chalmers in 1912, and in England in 1913 C. R. Box reported its occurrence at Slough ; others were described in Lymington, Cardiganshire, Manchester and Shropshire.

As regards possessions abroad, except in Egypt no extensive epidemics were recorded. C. G. Manning described in 1910 in Barbados a condition believed to be pellagra, under the name *psilosis pigmentosa*, in which there was severe stomatitis and food was refused ; it was accompanied by intractable diarrhœa and scurvy-like dark patches on elbows, knees and feet, and followed by mental symptoms. Death might be preceded by gangrenous areas on trochanters, sacrum and points of pressure. Five years later J. F. Siler, a member of the Thompson-McFadden Commission, noted how much the disease had increased in recent years in Barbados, spreading from Bridgetown practically all over the island, but affecting the native coloured population almost exclusively and more particularly women in later life. Some of the cases were of an acute type, and the death-rate varied in different districts between 7·5 and 13·3 per 10,000 population.

The symptoms regarded as characteristic, from the early days of the recognition of pellagra, one might say essential for diagnosis of this condition were dermatitis and pigmentation, diarrhœa and later dementia. Where the first and second were present and the third did not appear practitioners would designate the disease as pseudo-pellagra, pellagroid, or, if the first symptom was not in evidence, *pellagra sine pellagra—pell' agra* meaning, of course, rough skin. In 1928 connection was pointed out by Klauder and Winkelman, Sweitzer and, later in 1931, by Kumer, between pellagra and alcoholism, and alcoholic pellagra came to be looked upon as yet another variant. In 1935 Castellanos of Cuba de-

scribed a condition as the 'pellagroid beriberi syndrome' and Professor H. B. Day has recorded that beriberi in combination with pellagra occurs also in Egypt.

As long ago as 1763 Casal described the poor diets of those living in the pellagrous districts of Andalusia and actually ascribed the condition to faulty nutrition. Also, as has been pointed out, a variety of morbid conditions has been recorded from different parts of the world, ascribed vaguely to malnutrition, imbalance, diet deficiencies, and the presence of one or more of the symptoms of pellagra in these conditions has led to much discussion as to whether they were merely forms of pellagra, and, if we set out to clear the ground by attempting to define exactly what is to be taken as indicating pellagra—*hic labor, hoc opus est.* Dr. Hugh Stannus has done much to establish the foundations on clinical grounds from years of observation and it is from his publications on *Pellagra and Pellagra-like Conditions in Warm Climates* that much of the information here given is culled. The striking character of the skin manifestations has naturally led to stress being laid on them for differentiation, in fact the name itself implies as much. Strambio in 1789 noted it as a generalized affection in the following words which occur in his *De Pellagra*, published in Milan that year :

Morbus chronicus totius corporis nervorumque functiones potissimum lædens, ut plurimum cum desquamatione dorsi manum et pedum aliarumque ævi expositarum sive est syndromes eorum, quæ retulimus symptomatum, inter quæ præcipua et frequentiora sunt variæ affectiones cutaneæ, spasmi, dolores, vesaniæ.

That the cutaneous lesions were not essential to the clinical picture was known to Casal and to Strambio in the eighteenth century, because they mention *pellagra sine pellagra*, or, as Roberts stated as recently as 1912 but in worse Latin, *pellagra sine exanthemata.* As Stannus has said, the more we study the disease the more do we find gradations from the typical variety in individual symptoms, variety in course from mild to fulminating, reduction even to absence of individual symptoms, just as in other diseases, without negativing the diagnosis. It is difficult, therefore, *to* decide exactly where to draw the line. Angular stomatitis and glossitis are undoubtedly early signs in pellagra, but if properly treated they clear up. Consequently in some districts certain practitioners will diagnose all such cases as pellagra. The site and distribution of the rash was for many years, and is even now by some medical men, believed to be determined by the action

of the sun, from exposure to its rays. " Supprimez le soleil et vous supprimerez la pellagra," wrote Landouzy and Bouchard, yet we find the rash at times on palms and soles, on scrotum and vulva, and on the mucosæ of the mouth and tongue. Stannus's studies on the disease in African prisoners have demonstrated the marked variations of these lesions.

Again, the mental condition often associated may arise in the course of pellagra and may be late ; on the other hand pellagra by no means infrequently develops in the insane. The association that seems to exist between pellagra and the inmates of asylums was noted nearly a hundred years ago, in 1847, by Baillarger, and twelve years after him, in 1859 and again in 1865, E. Billod confirmed the frequency with which the insane were the subjects of pellagra.

Conditions which from the association of symptoms in a pellagrous district are diagnosed without hesitation in adults are not so easily decided in children, because there is, at least has been, a general notion that pellagra in the young is a rarity. J. Goldberger and G. A. Wheeler in South Carolina in 1928 found a large number among children between two and fifteen years of age ; Lavinder has recorded as pellagra even nurslings presenting diarrhœa, sore mouth and rash, and Fakhry in 1932 stated that he found children in Egypt very susceptible ; further, if they recover early or die early before the rash appears, how can we say with assurance that they were or were not pellagrins ? Stannus in 1925 and again in 1930 drew attention to epidemic outbreaks of glossitis and stomatitis in East African natives and suggested their relationship with pellagra, and, later still, reviewing the question in the light of modern knowledge, he is of opinion that all the following should be included in the term Pellagra :

1. Epidemic " central neuritis," described by Scott in Jamaica in 1918—Scott's palsy (see below).

2. Autumn stomatitis of Jamin at Tunis, 1925.

3. Epidemic glossitis, described by M. Nogue as occurring at Dakar and Senegal, also in 1925.

4. Glossitis and angular stomatitis in children at Sierra Leone, described by M. G. Blacklock in 1925.

5. A and B Avitaminosis described by E. J. Wright also in Sierra Leone, in 1928 and 1930 (see below).

6. Outbreak of glossitis and angular stomatitis described by J. Katzenellenbogen in 1928 among labourers in Palestine living on a monotonous diet of preserved food and legumes.

7. The condition known in the Seychelles as *decoquée*, described by J. T. Bradley in 1929, the chief symptoms being soreness at the angles of the mouth, soreness and redness of the eyelids, an erythematous

rash on the genitalia, in some patients affection of vision and hearing, and varying reflexes (see later the similarities between this and Scott's palsy as reported in Jamaica).

8. Keratomalacia among the Chinese at Peiping with xerosis of conjunctiva and cornea, nyctalopia, and cutaneous affection of face, neck and forearms, recorded by A. Pillat in 1929.

9. Kwashiorkor, an affection of children described by Dr. Cicely Williams in the Gold Coast in 1935. J. F. Carman called attention in 1935 to a similar condition occurring among the Kikuyu children in Kenya (see below).

10. Nutritional retro-bulbar neuritis in school-children particularly, observed by D. G. Fitzgerald Moore in Nigeria in 1934 (see below).

11. Nyctalopia, ulceration of the cornea, sore tongue, " butterfly patch " dermatitis and " Casal's necklace " observed by J. Harkness in Uganda in 1935. This brings us again close to the original descriptions of pellagra.

Some of these, though regarded now as probably variants of pellagra, show sufficient departures from the classical pellagra to warrant a little more detailed description.

First in order of time was the Spanish Town epidemic, the outbreak of so-called " Central Neuritis in Jamaica," sometimes dignified subsequently in text-books by the name Scott's palsy, which took place in 1917. The onset was sudden among the natives working on a sugar estate and very many were attacked, forty or more in a single day and altogether there were well over a hundred cases on this estate alone and subsequent inquiry revealed other cases in other parts of the island. The symptoms were conjunctivitis, redness and swelling of the eyelids, small ulcers and abrasions of the lids, photophobia, stomatitis and burning sensation in mouth and lips, aphthæ and fissures at the angles of the mouth. These symptoms were common to all, but two weeks later cases divided themselves into two distinct groups : One suffered with severe diarrhœa which might terminate in death from exhaustion, or in improvement and complete recovery ; the other with obstinate constipation and development of nervous symptoms, burning sensation in the toes and soles, with numbness and tingling extending up the legs, then inco-ordination and difficulty in walking, but without loss of power or objectively detectable sensory changes, except difficulty or inability to distinguish heat and cold ; knee-jerks absent, no wasting of muscles, a high-stepping gait, diminishing vision and hearing, which would become permanent in those who did not die.

Without going further into detail we may quote from the summary of the account. The onset in each case was sudden, the patients being attacked while at work and apparently in good

health ; the initial symptoms in each case were conjunctivitis and stomatitis and thereafter the patients could be readily divided into two categories, according as they exhibited intestinal or nervous symptoms, never both. The diet of those attacked consisted exclusively, or almost exclusively, of sugar-cane ; the Wassermann reaction with serum and cerebrospinal fluid was invariably negative ; the morbid anatomy and histology of the nervous cases was typical of a ' central neuritis ' ; fresh cases ceased to appear with cessation of the cane cutting.

Those with a much larger experience than the author have come to regard this condition as a variant of pellagra, but in his original monograph he argued against this diagnosis on the following grounds : That except for the sores of lids and lips there were no skin manifestations and none of the patients showed any mental symptoms and it appeared very strange that there should be an acute outbreak involving so many persons—well over a hundred —all of ' pellagra sine pellagra ' and the conclusion was drawn that it was more likely to be caused by some toxin, a point which was discussed in the original article. Mention, however, should be made of the fact that experimentally sugar cane has been found to precipitate the onset of pellagra or pellagra-like symptoms in animals on a deficient diet and, in connection with this outbreak in 1918, it is noteworthy that the diet of those attacked was almost exclusively sugar cane.

The condition described by E. J. Wright in Sierra Leone under the title of *A and B Avitaminosis*, in 1928, bears certain resemblances to the above ; the patients suffered from the same mouth and eye symptoms, with tongue tremor, sensations of heat, numbness, tingling, and impairment of sight and hearing, and, later, Rombergism (not present in the Jamaica cases), inco-ordination, ataxia and paresis (in the Jamaica cases there was no loss of muscle power). In these patients the staple food was rice and cassava, eaten with palm oil and dried fish—deficiency of Vitamin A.

The *decoquée* of Seychelles described by Bradley in 1929 is even closer in resemblance to the last than to the Jamaica condition. In *decoquée* the symptoms were soreness at the angles of the mouth and soreness and redness of the eyelids, an erythematous rash on the genitalia, varying reflexes, and, in some cases, affection of vision and hearing.

Kwashiorkor was the name of a condition described by Dr. Cicely Williams, observed by her in children from one to four years of age in the Gold Coast in 1933. In all cases she obtained

a history of deficient breast-feeding supplemented by maize products, locally known as arkasa and kenki. The condition took some four to twelve months for full development. Resemblances to pellagra were the presence of thickened dark patches on the ankles, knees, wrists and elbows, with slight œdema of the extremities, and there might be ulceration of the mucous membranes of mouth and eyes, and vomiting and diarrhœa with wasting were common; the temperature was irregular. There were, however, no nervous symptoms. Vitamin B was deficient in the diet and, if the disease was not too far advanced, recovery followed the giving of milk and cod-liver oil. It will be seen that there are indications of lack of vitamins A, B, and C, but exact correspondence with none individually. Possibly this disease is a transition between, or a combination of, known deficiency diseases. A like condition occurring among Kikuyu children of the same age in Uganda has been already mentioned.

Finally, Dr. D. G. Fitzgerald Moore described in 1934 and later a condition occurring in Nigeria, mainly in school-children, but not confined to them, among the poorly fed. The symptoms in this also were sore tongue and mouth, with aphthæ, itching rash on genitalia, and later dimness of vision, loss of central acuity and severe involvement of the optic nerve. The chief article of diet incriminated was gari, a food prepared from bulrush millet, so whether the disease is an avitaminosis or a toxic state or a combination of the two is a matter for further research. Moore has named it *Nutritional Retro-bulbar Neuritis*.

We see that by these gradual transitions we have got far away from ' typical pellagra ' and we are led to repeat the question : Where are we to draw the line? Fortunately this is more of a clinical than a historical problem and need not concern us further. Points deemed to be worthy of consideration from the aspect of the history of medicine have been presented above.

In concluding this section we may sum up by saying that the symptoms detailed appear to be indicative of diet deficiency ; that pellagra is also a condition of diet deficiency ; but it is a big step to take if we are asked to conclude that all are the effect of the same diet deficiency. Pellagra is found common among people living on a diet badly balanced and particularly on one lacking protein of high biological value and the somewhat hypothetical factor, the P.P. (pellagra preventing) fraction of Vitamin B, now called Vitamin G., but this association is not invariable and there is evidence of an intrinsic as well as of an extrinsic factor.

THE ÆTIOLOGY OF PELLAGRA

As already stated the first recognizable account of what was undoubtedly pellagra was that of Casal in 1762 ; to go back beyond that time would but involve us in vague surmise. The suggested causes assigned may be enumerated briefly by way of introduction to a consideration of its ætiology. In 1780 Gherardini stated that the chief cause was bad food and, more especially, bad maize. Eight years later F. Z. Jansen supported the bad food idea but would not limit it to maize, holding that any cereal which was in a mouldy state might cause the disease, and the following year G. Strambio agreed but added further that any depressing influence might be a predisposing factor. In his *Dissertazioni* mentioned above (p. 912) Strambio relegated cases to three clinical types—intermittent, remittent, and continuous. As ætiological factors he notes any ' depressing influence,' bad food, maize of poor quality, the use of rancid oil, and he observed some relationship between dry, hilly places and this disease. He thought it was hereditary but not contagious. He observed—and was probably the first to do so—that pregnant or nursing women were prone to develop it, and also that the disease might occur without the cutaneous symptoms, till then regarded as characteristic—*pellagra sine pellagra*. Iu 1791 L. Soler stressed the predisposing effects of poor surroundings and depressing influences and ascribed pellagra to general poverty, wretchedness and dirt, and Thouvenel to maize not properly matured. For the ensuing eighty years the ' maize theory ' held the field ; all those of note who contributed to the literature of the subject were whole-hearted supporters of it ; among them may be mentioned F. L. Fanzago (1807), G. B. Mazari (1810), Guerreschi (1814), L. Balardini (1845) and C. Lombroso (1870). Having observed many cases among alcoholics, or, maybe, many pellagrins became addicted to drink, J. B. Calmarza writing from Spain in 1870 ascribed the disease to ' misery and alcohol.' Others supported him, finding difficulty in reconciling the existence of pellagra symptoms and alcohol with the maize theory and hence there came into vogue the terms parapellagra, pseudo-pellagra and alcoholic pellagra.

From 1880 onwards we note the tendency to ascribe conditions of obscure nature to bacteria, as already seen in malaria, yellow fever and beriberi. In 1881 Majocchi thought that *Bacterium maydis* was the cause ; twenty-one years later (1902) Ceni ascribed it to an Aspergillus, and in 1904 Fossati found a streptothrix,

Tizzoni in 1908 a streptobacillus.   Within the last decade naturally a virus has been suggested, by W. Susman in 1927 and by B. R. Tucker in 1935. Briefly, the character of the organism has changed with change of fashion and progress of the science of bacteriology.

From time to time insect vectors have been thought to convey infection ; ticks, lice, bed-bugs, fleas, Tabanidæ, Simuliidæ, and others. What they conveyed was for the time being ignored. On general grounds they became discredited ; thus the bed-bug is almost universal yet pellagra is endemic, and the sex preponderance in women would be left unexplained. Simuliidæ as carriers, a theory favoured by Sambon, are absent from Barbados where pellagra is not uncommon. Sambon went even further in his surmises and thought that the evidence favoured a causative protozoon. In summing up the points in support of this and against the maize theory (see later) he remarked in 1910 that pellagra was rare, even absent, in some places where maize was the staple food of the people and that it occurred in places where maize was not eaten ; that the disease might recur each spring even after the patients had removed from the endemic area ; that some of the symptoms, for example, the skin eruptions, and later nervous complications were analogous to those of trypanosomiasis and syphilis ; that blood examination revealed an increase in large mononuclear leucocytes, as in malaria, and, finally, that the disease, like trypanosomiasis, malaria and syphilis was favourably influenced by arsenicals.

When Simulium was ruled out Sambon next thought that Stomoxys calcitrans might be the vector, for it is a common insect in pellagra countries, it visits human dwellings, attacks several hosts, one of which is man, and it bites during the day and this might account for the women, engaged in household work, furnishing a larger proportion of cases.

Some have urged that the disease is contagious, but evidence to the contrary is strong and when several cases occur in one family or one house it is usually impossible to exclude common source of origin. Active intercourse between healthy townspeople and country people suffering from the disease did not result in the former acquiring it.   Still less evidence is there of heredity ; such evidence as was brought forward was capable of other explanation.   The Piedmontese Commission came to the conclusion that there was a dyscrasia or ' congenital tendency '—si nasce pellagrosi.   They found 189 such among 927 cases, 20·3 per cent., Lombroso found 74 out of 472, or 15·7 per cent. Maragliano,

in 1879, placed it a little higher, 26 out of 150, or 17·3 per cent.

An investigation was made of 815 pellagrins in asylums and 415 of them, or 50·9 per cent., had had pellagrous parents. Boudin in 1861 found among 657 married couples with 740 pellagrous children that in 15 per cent. of cases both parents had been affected, the father only in 24 per cent., the mother only in 27 per cent. In 18 per cent. both parents were healthy although the children were pellagrous. This, however, loses much of its weight when we find that the children had not been removed early to places where pellagra was not endemic, but had remained subject to the same general conditions as regards environment and food as their parents. Further, in many pellagrous districts even babies at the breast are given polenta also.

The suggested causes above enumerated have little more than passing historical value ; we may say in general that the disease seems always to be associated with inadequate food, or nutritional imbalance, and poor living ; it is commonest in and almost restricted to the poorer rural or agricultural populations.

The food incriminated was maize for the disease was reported first from Spain where maize had been introduced from America ; thence it had been taken to Turkey and from there to Italy about the middle of the sixteenth century and during the next hundred years was extensively cultivated there. Thence it was transported eastwards across Europe to Hungary, Rumania (in 1710) and Greece, reaching Egypt in 1847. France started growing it early in the nineteenth century, somewhere about 1810. As the cereal became the common food, so were cases of pellagra reported, the spread of the disease followed the extended introduction of the maize. On the other hand, though maize had long been eaten in the United States cases were not reported there in any number till 1909 ; in the following years it became very rife among the negroes and the poor whites in the Southern States, 170,000 cases being recorded in 1917, and the fatality rate was high.

Zeism, or the maize theory of the origin of pellagra, held the field for a very long time. The most popular view was that the symptoms were the result of a toxic process arising from damaged maize, possibly allied to ergotism from contaminated rye. The points adduced in favour of this were mainly three : First, that the disease was endemic only in countries where maize is the staple food of the peasantry, polenta in Italy, conchade in Gascony, mamaliga in Rumania, whereas cases were rare in districts near by where maize was less used. An official report of 1879 stated :

La causa d'una relativa immunità nel Cadore e nell' Agordino viene spigata del modo alquanto diverso d'alimentazione di quegli alpigiani ai quali la richezza dei boschi rende meno disgraziabia la vita, potendo essi, oltre della polenta, cibarsi di patate, d'orzo, fugioli e latticini in piu larghe proporzioni degli altri villici della provincia.

Secondly, there is no evidence that pellagra was observed anywhere in Europe till after the introduction of maize, and even then a long enough interval elapsed for maize to become a staple food of the people concerned. As stated above, it was brought to Spain from America, but it was not widely cultivated until the second quarter of the sixteenth century. Italy seems to have obtained it, not from Spain as would be expected, but from Turkey, for when it was introduced into Italy it was known as *grano turco*, and by the middle of the seventeenth century was widely cultivated in that country.

The third point in favour of the maize theory was that provision of other food and reduction or prohibition of maize was succeeded by diminution of prevalence and in early cases by cure.

On the other hand, there is no doubt that maize cultivation has been very widespread and the cereal is largely used for food, nevertheless the area of prevalence of pellagra is in proportion small ; further, that it had been used for years, apparently without harm, before the disease made itself known. This is not a strong point because it might be widely used without being the *staple* article of diet, as the zeists maintained. Of greater weight is the fact that sporadic cases occur among people who do not eat maize as a usual food. This was met by the zeists affirming that such cases had been wrongly diagnosed, or, to use Roussel's term were " arbitrarily made up groups of symptoms in which nervous and psychical affections are included with disorders of the digestive organs and with morbid appearances in the skin, and the name ' pellagra ' given to them," briefly they were *unités factices*. The difficulties created by classing all such as pellagroid or pseudo-pellagra have not yet been cleared up, although half a century and more has passed since Dejaune wrote, in 1871 : " There are maladies differing widely among themselves, and all of them very different from endemic pellagra, not only in the ætiology, but also in the nature and concatenations of the symptoms."

Four years previously, however, Bouchut had suggested that grain other than maize might perhaps undergo similar changes and so give rise to pellagra in places where maize is not grown at all or is not the main food.

F. M. Sandwith was a staunch supporter of the maize theory,

speaking concerning Italy and Egypt; in these countries, he said in 1910 that where maize was not cultivated and eaten extensively pellagra did not exist, but that maize might be cultivated widely without pellagra existing and consequently he was convinced that the disease was due to the habitual use of *damaged maize.*

So far, beyond the fact that cultivation and extensive use of maize as food seemed to be associated with prevalence of pellagra nothing very tangible in the way of knowledge of the causation of the disease had been attained. In the meantime certain investigations had been going on and were now pursued with greater energy.

Lombroso's theory, in which others shared and which is held in some parts of Italy even to-day, was that the symptoms were due to a toxin which developed in deteriorated maize. In 1905 Aschoff, having observed that the cutaneous lesions of pellagra were most marked on those parts which were exposed to sunlight, and secondly that hogs and sheep fed largely on buckwheat developed skin lesions on exposed parts, postulated his *photodynamic theory*, which was that in maize there was some photosensitizing substance, and some five or six years later Horbaczewski experimenting with small rodents tried to demonstrate such a substance, but his findings were not confirmed.

As often in scientific investigation the more the problem was studied the greater became its complexity. That pellagra was not due merely to low nutritive value of the diet was clear because (the same argument, it will be remembered, was applied to beri-beri) in malnutrition, marasmic states and starvation pellagral symptoms do not appear; nay more, pellagrins often look well nourished, and people living largely on rice and potatoes—according to the standards of the day less nutritious than maize in protein, carbohydrate, etc., content—do not suffer from pellagra. It was argued, therefore, that if there were any direct causal connection between maize and pellagra it must be some acquired property, due, it might be, to decomposition, damage or disease, and research was then directed to discovery of the nature of this.

One theory was that in place of its natural habitat and growth in sand or the loose loam of the tropics, the soil in temperate climates was poor and the product in consequence 'prone to decompose'—purely an hypothesis; or that it was cut before it ripened or was gathered before it had dried and so became putrid, or if stored in a damp state moulds were likely to grow on it. Evidence of an epidemiological character adduced in support of this was that the Wallachian peasantry of Transylvania had a

diet of maize-polenta, but allowed the maize to ripen thoroughly and dry on the ground before being stored in barns, whereas those of Rumania did not wait for it to ripen but cut it early and threw it into pits where it became musty. The latter suffered much from pellagra, the former did not. Further, if the maize harvest was bad, there was almost certain to be an increase in pellagra and the disease might actually become epidemic.

The evidence seemed to favour some injury to or spoiling of the maize and the next question was as to the nature of the injury or damage. Balardini in 1845 thought it was a toxic parasitic mould, greenish in colour—verderame—analogous, as already stated, to ergot in rye, and experiments carried out with it on animals (fowls) seemed to support the hypothesis, but this mould was found often to be present on maize in districts where pellagra was at least uncommon if not actually unknown. Nonetheless, the idea was held for some time and supported by the French Commission of Inquiry. Lombroso, twenty-five years later, in 1869 and onwards, studied the matter afresh, confirmed Balardini's findings with decomposed maize, but, since verderame was often not found, he concluded that the disease was due to " certain substances developing in the parenchyma of the decomposing corn " (compare the opaque grains of rice as causing beriberi), probably a ' fatty oil ' and an extractive not found in good maize and resulting from a fermentative process. This opinion gained wide support, reserve being maintained as to how the fatty oil and extractive were formed, whether or not by organisms already present in the grain. (In the elucidation of the cause of pellagra we constantly see lines of thought running parallel with those on beriberi.)

Stannus in 1911 and Sheppard in 1912 showed on clinical and epidemiological grounds that maize was not a conditio sine qua non, but that pellagra occurred among rice-eaters ; later, W. H. Wilson showed the same for communities subsisting largely on millet.

In 1913 the United States Bureau of Public Health set up an investigation into an outbreak in the Southern States, with J. Goldberger at the head. Studies in the field demonstrated the prevalence of the disease among the very poor, though those attending on them were not attacked. The diet of the people concerned, who worked mainly in the cotton fields, contained very little protein of an animal source, but consisted very largely of cereals. Again, at an orphanage in Missouri the disease broke out, but only among those of a group living on a diet containing

very little animal protein, and at other orphanages it was common among children living on a cereal diet almost exclusively, not only maize. When milk and eggs were added, the pellagra disappeared, but in others where the change had not been made there was a large percentage of recurrences the succeeding year.

·W. H. Wilson in Egypt made similar observations and the conclusion was drawn that as the giving of proteins of high biological value prevented recurrences, the absence of them favoured or precipitated the disease. This was the *Amino-acid deficiency theory*. Analysis of maize protein, zein, showed it to be deficient in lysin and tryptophane. In reply to those who suggested that maize germinating from being stored in a damp condition was the cause the experiments of Carranca and Trujillo, carried out in 1929, are of interest. They kept maize in a moist atmosphere until it germinated ; then washed it, triturated it to a paste, added sugar and water and gave it in quantities of 50–60 grammes daily to pellagra patients " with very good effect."

Milk and meat having proved potent prophylactically against relapse, yeast was tried—it had previously proved effective in black tongue of dogs, a condition regarded as the analogue in animals of pellagra in man—and an acid yeast extract was prepared which contained very little protein nitrogen and was found quite as efficacious. As a result there was postulated a non-protein pellagra preventing factor (P.P.) in yeast and other foods which had proved effectual—a yeast vitamin, which was shown to differ from the antineuritic Vitamin B. This was known as B_1 and the P.P. factor B_2 (later G) and people living on the borderline of insufficiency might, on further reduction of protein intake, suffer from pellagra.

One of the chief difficulties which none of the strictly ' maize theories ' explains is the occurrence of pellagra in certain individuals or groups and its absence from others on the same diet. E. H. Clewer studied the disease in 1928 among the maize-eating natives of South Africa. Cases were observed among Durban prisoners but not in others, though the diet scale was the same in all. The hypothesis is advanced that a diet generally deficient in Vitamin B_2 or the P.P. factor leads to the production of a ' subpellagric state ' which some subsidiary factor may convert into true pellagra ; one such, it is suggested, is hard work in bright sunlight to which Natal prisoners are put. Since pellagra is not restricted to prisoners, however, it is probable that many of the natives are ' sub-pellagrins ' and a monotonous diet together with hard work while they are exposed to the sun tips the scale. He

recalls to mind an analogy in scurvy among Bantu labourers in the Transvaal mines.   On arrival they appear to be healthy in spite of the fact that their usual diet is deficient in antiscorbutic value.   Hard work underground, though they are on a liberal diet, may be followed in a few weeks by symptoms of scurvy.

At the same time as this study was being carried on in South Africa Dr. H. Chick was showing by research at the Lister Institute that the skin lesions ascribed to lack of the P.P. factor of Vitamin B were due to variations in the basal diet caused by incomplete purification of the caseinogen used as the source of protein.   When caseinogen had been elaborately purified the skin lesions developed consistently on a diet whose sole deficiency was in Vitamin B_2. Caseinogen and other substances of a protein-like nature appear to absorb this vitamin and the high nutritional value of casein as a protein may be due, not only to the nature of its amino-acid constituents (v.s.), but also to the fact that it may contain Vitamin B_2 as a contamination.   It is thought that this may explain why Goldberger obtained disappointing results in the prevention of human pellagra when large daily doses of purified casein were tried, while milk, skim milk or butter milk proved of great value.

As the Medical Research Council Special Report of the Vitamins (1932) states, in trying to throw light on the vexed subject, it may be that

Maize contains a positive ' pellagra producing ' factor, perhaps operative only in the absence of the P.P. factor . . . the action of the P.P. factor might be to neutralize a toxin rather than make up a deficiency, just as vitamin D ' neutralizes ' the anticalcifying effect of certain cereals though it also·makes up a deficiency.

It will be seen that, as regards discovery of the actual cause, we have not, in spite of all the research that has been carried out, advanced very far.   We know, and have known for nearly a century, that pellagra is associated with a poor and monotonous diet, and that dietetic changes can prevent it, but we cannot be said to know much more.   Stannus recently, in 1936, in reviewing the situation lays stress on the fact that maize theories have held the field for a long time because in endemic parts of Italy particularly it is eaten in the form of polenta or as maize meal made into a heavy unleavened bread as the staple food.   In the United States the indigestible corn-mush is a sort of polenta, and the popular corn-bread and hoe-cake are, in pellagra areas at least, rarely adequately cooked.   It is time, writes Stannus, that pellagra should be freed from the maize millstone which has hung about its neck for so many years.   The eating of maize by white races

has connoted poverty. The same author, in 1910, 1912 and 1913 recorded an outbreak of typical pellagra among central African natives living on a diet of rice and beans. He regards the basic cause as an ill-balanced or inadequate diet with consequent gastritis. The maize theory, apart from other reasons, leaves unexplained the important fact that many native races living on a diet chiefly consisting of maize suffer little if at all from pellagra. Generally, the preparation of flour, whether of maize, cassava or other, by the natives is an elaborate process. When it is ill- or hastily prepared, as in parts of the Gold Coast, we may see the condition spoken of above, kwashiorkor (regarded by Stannus as a variant or form of pellagra), or the retrobulbar neuritis and optic atrophy described by Fitzgerald Moore in Nigeria. That other concomitant deteriorating factors may play a part has been held since the end of the last century when, in 1898, Sandwith noted the association of pellagra and ankylostomiasis in Egypt, and Long, in 1910, the presence of protozoal and helminthic infestations.

To sum up :

Many cases outside endemic areas pass undiagnosed because the so-called triad of classical symptoms, dermatitis, diarrhœa, dementia, are [sic] not in evidence. Conditions designated pseudo-pellagra, parapellagra, alcoholic pellagra, secondary pellagra and pellagroid should also be grouped as forms of pellagra.

Maize plays no specific part in the ætiology, and there is no satisfactory support for any of the theories postulating a specific infective agent. Deficiency of biological protein *per se* is not the cause, and further there is no convincing evidence that pellagra is a simple avitaminosis. It may be due to failure in one or both of two factors, an extrinsic in the diet and an intrinsic in the alimentary canal, as postulated as resulting in pernicious anæmia, the extrinsic being commonly present in foodstuffs containing protein of high biological value and the vitamin B complex. The presence and distribution of the exanthem in pellagra is determined by several factors, such as pre-existing changes in the skin due to trauma which may be of several kinds, and to the vascular condition of the parts involved (Stannus).

There is a danger, when undertaking research on ' deficiency diseases ' or diseases ascribed to lack of some essential food factor, of our making the experiments connected therewith a little too exact, and we must be cautious in applying the results to circumstances as we meet them under natural conditions in the field.

How many are the obscure phenomena of disease which are traceable to faulty food ; how well it is, in the experimental study of nutritional problems, to depart sometimes from the use of so-called synthetic diets deficient, or supposedly deficient, in a single food factor, and to employ for such studies the ordinary food materials used by the

man in the street or by the stock laboratory animal, in both of whom obscure phenomena of ill-health so often appear ; how instructive it is to work at times with diets which are not wholly lacking in a given food factor, but in which an insufficiency of one or of several is combined with food faults of another order, such as lack of balance in proximate principles . . . how necessary is an adequate supply of all [the vitamins] to the maintenance of nutritional harmony and how readily is this harmony disturbed by the insufficient supply of any one of them ; how variable may be the reports of equally competent observers relating to a particular vitamin defect, and how much do these reports depend upon the composition of the diets and the age and strain of the experimental animals, as well as on the conditions of climate and altitude in which the different observers are working ; finally, how important it is to recognize that complete deprivation of any vitamin is not a matter with which the physician is greatly concerned in practice, though he is often confronted with an insufficient supply of one or other or several of them in diets often faulty in other regards (McCarrison).

The following notes, based on the reports collated by H. S. Stannus, are of interest historically and epidemiologically in showing the prevalence in the past and at the present day of pellagra and allied conditions in warm climates :

Africa :

1847   F. Primer gave the first description of cases in Egypt.

1851   Abeille found cases among Arabs near Calle in Tunisia.

1865   A. Figari recorded " leprous pellagra " as a venereal disease in Lower Egypt.

1880   J. de Pietra Santa described pellagra in Algeria.

1906   Some 150 cases (L. G. Haydon) among Zulu prisoners in the Natal rebellion.

1911   H. S. Stannus recorded an outbreak among the prisoners at the Zomba Central Prison, Nyasaland.

1912   Outbreak of ' zeism ' in the Victoria Gaol, Northern Rhodesia, reported by P. A. Nightingale.

1912–13   Outbreak in the Mental Institution, Pretoria, and thereafter occasional cases occurred in different parts of South Africa. J. Drummond recorded a case at Durban in 1913 and another in 1920.

1928   A. J. Boase noted ten cases among native prisoners at Lira, Uganda ; ten also at Kampala and seven at Entebbe.

1929   E. H. Clewer recorded an outbreak at Durban Prison, sixty-four cases. Diet was mealie meal, rice, meat or beans, vegetable curry, bread and soup (see above, p. 925).

1930   A. McKenzie, four cases in Songea district gaol, Tanganyika ; there had been only one in the preceding decade.

1933   C. Williams reported cases of kwashiorkor (see p. 917), a " nutritional disease of childhood associated with a maize diet," at Accra, Gold Coast.

1935   J. F. Carman described a similar condition among Kikuyu children in Kenya.

Recent reports from the Medical Departments of the Colonies and Dependencies in Africa record the presence of pellagra in the Gambia, Kenya, Nyasaland, Northern Rhodesia, Zanzibar, Basutoland, Bechuanaland and Swaziland. There is no mention of it in late reports from Sierra Leone, Nigeria, Tanganyika, Somaliland, Mauritius or the Seychelles.

India :

1925 Occasional case at Dichpali, Hyderabad, Deccan, and again in 1931 and 1933.

1927 J. W. D. Megaw and J. C. Gupta, on information obtained by a questionnaire to civil surgeons, reported that cases of actual pellagra were few in India, but the former in a later paper (1936) noted that there were nearly 3,000,000 cases of night-blindness.

1933 T. K. Raman recorded four cases at Guntar and stated that none had previously been described in Madras Presidency. The same year a case was reported in Bombay by B. H. Rajadhyaksha.

.1935 Cases at Lahore (S. N. Gupta), at Calcutta (G. Panja) and Poona (N. S. H. Mody).

Ceylon :

None reported though it was looked for by Dr. Lucius Nicholls who was well acquainted with the disease in the West Indies.

China : Records of cases are few.

1923 Case at Wuhu recorded by S. C. Wu.

1925 Outbreak in the Leper Asylum, Kona, and again in 1933 recorded by R. M. Wilson.

1927 One at Peiping recorded by Mu Jui Wu ; others were recorded there in 1930 by C. S. Ying and C. K. Hu. Also one at Honan, recorded by A. C. Lambert.

1932 Twenty-four cases recorded in the Hong Kong Annual Report of the Medical Department.

1934 Thirty cases in the army camp at Nanking.

Japan :

1925 M. Itoh recorded finding references to sixty cases and he himself had seen twelve. These were not found in the north islands but on the mainland of Korea and Formosa.

1929 S. Takahashi noted that seventy cases had been recorded in Japan and four more recently at Hokkaido.

Philippines :

1910 Case seen by D. D. Willets referred to by Rodriguez when in

1930 He published an account of another case. Clearly the disease is rare in these islands, but T. Dychitan described the same year a condition called *lapnus* as being common in Mindoro island, characterized by burning sensation in the soles, gastralgia, pyrosis and stomatitis, corneal opacity and mental symptoms, which is very probably pellagra.

Siam :

> Doubtful ; at all events exceedingly rare. A man suffering with glossitis, dermatitis of hands and feet and scrotum, with diarrhœa and a " polyneuritic gait " was recorded by R. W. Mendelson in 1923 as possibly a mingling of beriberi and pellagra.
>
> It may here be mentioned that in 1935 Castellanos of Cuba described a condition of the " pellagroid beriberi syndrome."

Malaya :

> Sporadic cases do occur but they are not common ; no outbreaks have been recorded. W. S. Sheppard of Singapore states that they may be mild and he thinks that many such escape recognition.

Dutch East Indies : Rare.

1931 W. G. Bosch reported a case in Java.

1935 C. D. de Langen and B. Djohan reported one in Sumatra.

Australia :

1927 S. J. Cantor recorded five cases in Melbourne with the rash and mental symptoms indicative of pellagra.

1928 N. Paul reported one in Sydney.

Central America :

1882 Cases reported by D. Nibbi in Mexico. According to R. Romero, writing in 1931, it is common among the half-breeds of Yucatán. In the decade 1921–30 he states that at Mérida, among a population of 80,000, deaths have been 49, 71, 22, 81, 70, 91, 72, 29, 23 and 21 respectively. Ganmer places the incidence at one in ten.

Pa amc Canal Zone :

1909–11 Thirty-two cases were diagnosed during this period.

West Indies :

> According to recent Medical Reports pellagra exists in Trinidad and Tobago, St. Christophers, Nevis, St. Lucia, Antigua, Jamaica, Barbados and British Honduras.
>
> It was first reported in Jamaica by D. J. Williams in 1897, and in 1905 some 4 per cent. of the 1050 asylum inmates were affected. In Barbados it was first described by C. G. Manning in 1909 as *psilosis pigmentosa*. In Porto Rico five cases were recorded by Velarde among 475 patients admitted to hospital in 1931-2.

D. SCURVY

Scurvy can hardly be called nowadays a disease of warm climates, for it has of recent years been a commoner occurrence in expeditions to the arctic and antarctic, as in Captain Nares' expedition with the *Alert* and the *Discovery* in 1875 and the Jackson-Harmsworth expedition to Franz Josef Land in 1894–7,

and among armies and the inhabitants of besieged towns, as in Breda in 1625 when 1608 cases of scurvy were recorded, or the siege of Thorn in Prussia in 1703 where more than 6000 of the garrison and many of the inhabitants are said to have perished through it ; in fact, the town was surrendered to the besiegers on account of the ravages of scurvy.

In the opening chapters of this work we spoke of its prevalence among seamen and said that any voyage of six weeks' duration, and sometimes even less, was almost invariably complicated by scurvy and many a promising expedition was ruined thereby. Almost any voyage of discovery during the 300 years 1497–1795 was liable to be brought to naught by reason of it. Since voyages in the sixteenth to eighteenth centuries were usually to tropical and sub-tropical regions, scurvy, from the historical point of view, must be included here.

There is no need to repeat what has been written in the section dealing with conditions in the Navy (see p. 21) and the successful voyages of Captain Cook, the success being in great part due to the absence of scurvy and the precautions which he enforced, based on 'the work of James Lind.

The association between mariners and scurvy is illustrated in the old French chanty reproduced below ; whether the English interpolations are due to the British adopting the chanty for their own or to the French acquiring a few words of English we cannot say.

> Plus d'un laissera sa peau
> Goodbye, farewell,
> Goodbye, farewell !
> Adieu misère, adieu bateau,
> Hourra ! oh ! Mexico !
> Ho ! Ho ! Ho !
> Et nous irons à Valparaiso
> Haul away, hé !
> Oula tchalez !
> Où d'autres laisseront leurs os
> Ha ! l'matelot !
> Hé ! Ho ! Lisse hé ! ho !

We do not hear of scurvy, at least we cannot recognize it, before the time when long voyages came to be undertaken, not, in fact, before the end of the fifteenth century, when Vasco da Gama sailed, in 1497, to the East Indies *viâ* the Cape of Good Hope. It is recorded that out of 160 men 100 died of scurvy. After this every voyage of any duration makes note of this disease. Thus, Lind tells of four vessels leaving England in A.D. 1600

for Bombay to establish ports for the East India Company and having 480 men besides officials and merchants. On three of the ships scurvy played havoc and 105 of the crews died of it which so reduced their numbers that passengers had to do seamen's work. Lind states that the other ship, on which was the Commodore, escaped because each man received three tablespoonfuls of lemon-juice thrice daily. The voyage to the Cape in this case occupied four months.

It seems strange that the East India Company was quite cognizant of the prevention of scurvy by oranges and lemons from the very beginning of the seventeenth century and these were carried as part of the regular supply from the year 1600 onwards; nevertheless the Navy did not adopt the principle for nearly two centuries, till 1795. Sir James Lancaster, who was in command of the East India Company's fleet in 1591, mentions scurvy being rife and no reference is made as to remedies or prevention; but from 1601 they formed part of the statutory issue. Sir Richard Hawkins, however, knew of the benefits of oranges and lemons ten years before, when he sailed to Brazil. According to the Dutch physician Ronsseus who wrote of the disease in 1564, sailors used to cure themselves of scurvy by eating oranges and lemons as soon as they reached the coast of Spain, and Woodall, who was a contemporary of Lancaster, gave lemon-juice a prominent place in his book, the *Surgeon's Mate*, published in 1617.

Ronsseus' actual words, in his second letter, Epist. II, are:

Nam et ea, quæ secundum methodum sunt, omittamus novimus nonnullos, qui solo pomorum aurantiorum unà cum corticibus usa sanitatem recuperarunt. Quod etsi empiricum sit, cum ipsa tamen ratione nonnihil habere commune videtur, siquidem quum in lienis affectibus, authore Galeno, opus sit attenuantibus pharmacis, citra manifestam aliquam caliditatem, cum modica astrictione, ut robur addatur affectæ particulæ, aurantia affectio lieni non prorsus inutilia pronunciabimus. Incidunt etenim, compescunt æstuantem sanguinem, et robur addunt læsa parti. Cæterum num ratione duce, homines barbari, ad propellandam hanc luem aurantilis primum usi fuerint, pro incomperto est : mihi probabilior ea videtur opinio, quæ fortuitò, et casa quopiam facultatem hanc compertam esse asserat, rediuntibus ex Hispania Batavis nautis, ac uberi novitate aurantiorum allectis, præter spem avida quadam gilositate morbum pellentibus, atque id non semel felici successu experientibus.

The following is a translation:

To say nothing of the remedies regularly employed in practice, we know of some people who have recovered their health, solely by taking oranges, skin and all. Although this is empirical it seems to be not without reason, for inasmuch as in cases of diseased spleens we

need, according to Galen, reducing drugs without obvious heating qualities, together with some astringent action so that the part affected may be strengthened, so we would say that oranges are not altogether useless in cases with diseased spleen. For they arrest the excessive flow of blood and give strength to the affected part.

Nevertheless, it cannot be ascertained whether foreigners, guided by reason, first used oranges to ward off the disease ; to me it seems more likely that this property was discovered accidentally by some Dutch sailors who, returning from Spain, were attracted by the novel richness of the fruit and by their greed and gluttony unexpectedly drove out the disease and had this happy experience not on a single occasion only, but repeatedly.

Again, John Winthrop in his *History of New England*, 1631, tells of the ship *Lyon* arriving at Boston in February of that year, and writes : " The poorer sort of people . . . were much afflicted with the scurvy and many died, especially at Boston and Charleston : but when this ship came and brought store of juice of lemons, many recovered speedily."

Winthrop also advised his wife, who was in England but was preparing for a voyage to America, to bring with her " a gallon of scurvy grass to drink." According to some authorities Scurvy grass is *Cochlearia officinalis* ; according to others *Barbarea præcox* or yellow rocket. Both belong to the Cruciferæ, and the latter is of the winter-cress genus, the leaves of which are used as salad.

It was known even in the early days that insufficiency of vegetables and green food played an essential part in causation, for trial was repeatedly made of dried vegetables, " a magazine of dried spinach prepared in the manner of hay " was boiled with water and mixed with the other food, but proved ineffectual in warding off the disease. Bachstrom in 1734 in his work *Observationes circa scorbutam ; ejusque indolem, causas, signa et curam* noted that abstinence from fresh and green vegetables was followed by scurvy and return to them resulted in cure.

One of the most disastrous voyages in history, disastrous from the prevalence of scurvy, was that of Lord Anson round the world in 1740–4. Five ships set out in September ; only one returned and of the personnel only one in twenty.

Soon after passing Straits Le Maire the scurvy began to make its appearance among us. And our long continuance at sea and the fatigue we underwent, and the various disappointments we met with had occasioned its spreading to such a degree that at the latter end of April there were but few on board who were not in some degree afflicted with it. And in that month no less than forty-three died of it on board the *Centurion*. But though we then thought that the distemper had arisen to an extraordinary height, and were willing to hope that

as we advanced to the northward its malignity would abate, yet we found on the contrary that in the month of May we lost double that number. And as we did not get to land till the middle of June, the mortality went on increasing so that after the loss of above two hundred men, we could not at last muster more than six foremast men in a watch capable of duty.

The havock which this dreadful calamity made in those ships was truly surprising. The *Centurion* from her leaving England, when at this island (Juan Fernandez) had buried 292 men and had but 214 remaining of her complement. The *Gloucester*, out of a smaller complement, buried the same number and had only 82 alive.

We see the contrast between this and Captain Cook's voyages only thirty years later, when in his second voyage, 1772–5, which lasted three years and eighteen days under all changes of climate he lost only four men (and one only on account of sickness) and three of these were in a precarious state—it is thought that they were consumptive—when they left England, and the *Discovery* did not lose any, although the voyage lasted four years two months and twenty-two days.

Less than three years after Anson had returned from his voyage Lind was making his experiments which have become classical; he writes:

On the 20th May, 1747, I took twelve patients in the scurvy on board the *Salisbury* at sea. Their cases were as similar as I could have them. They all . . . had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in . . . a proper apartment for the sick in the forehold, and had one diet common to all, *viz.*, water-gruel sweetened with sugar in the morning, fresh mutton-broth oftentimes for dinner ; at other times light puddings ; boiled biscuit with sugar, etc., and for supper barley and raisins, rice and currants, sago and wine, or the like.

Two of these were ordered each a quart of cyder a day. Two others took twenty-five drops of *elixir vitriol*, three times a day, upon an empty stomach ; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfulls of vinegar three times a day upon an empty stomach ; having their . . . food well acidulated with it, as also the gargle for their mouths. Two of the worst patients . . . were put under a course of sea-water. Of this they drank half a pint a day. . . . Two others had each two oranges and one lemon given them every day. . . . They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients took the bigness of a nutmeg three time a day of an electuary . . . made of garlic, mustard-seed, radraphan, balsam of Peru and gum myrrh ; using for a common drink barley-water well acidulated with tamarinds.

. . . the most sudden and visible good effects were perceived from the use of the oranges and lemons [the experiment would have had even greater scientific value had he given lemons to one and oranges to

the other], one of those who had taken them being at the end of six days fit for duty. . . . The other was the best recovered of any in his condition, and being now deemed pretty well, was appointed nurse to the rest of the sick. . . . Next to the oranges, I thought the cyder had the best effects.

Except that those who used the elixir of vitriol had cleaner mouths none of the other measures brought about any amelioration.

Sir Gilbert Blane has a great deal to say about scurvy in the Navy, but Captain Cook had demonstrated how successful measures of prevention could be and Blane really adds nothing more. Dr. John Harness, who was Medical Commissioner of the Navy at the beginning of the nineteenth century was chagrined at the omission of his name and in 1816 wrote to Blane remonstrating at this and saying that he (Harness) had used citric acid and lemons for the personnel of the Mediterranean Fleet in 1793.

In spite of all Lind had written on the subject and in spite of the influence which one would think his association with and standing in the Navy would have, in the late years of the eighteenth century thousands of cases of this disease were noted annually in the Navy and many years passed, some say nearly 100, after Lind's work was published before the issue of lemon-juice was made compulsory. There is some doubt as regards the actual year. Naval records state that Blane recommended the issue in 1793 and that it became an essential part of the naval dietary in 1796 (according to some 1795) when Sir Gilbert Blane was one of the Commissioners of the Navy Board. Others state that it was made compulsory in 1844, drawing a distinction between its being scheduled as ' an essential part ' and its being ' made compulsory.' Whether the seamen were compelled to take it or not there is no doubt that the majority did so for, by the early years of the nineteenth century scurvy, had become a comparatively rare disease in the Navy.

John Woodall, author of the *Surgeon's Mate,* has been referred to above (pp. 30, 932). In 1617, nearly 200 years before lemon-juice became a regular Naval issue, he wrote :

The juyce of Lemmons is a precious medicine and well tried, being sound and good, let it have the chiefe place, for it will deserve it, the use whereof is : It is to be taken each morning two or three spoonfulls, and fast after it two hours, and if you add one spoonfull of Aquavitæ thereto to a cold stomach, it is the better. Also, if you take a little thereof at night it is good to mix therewith some sugar, to take the syrup thereof is not amisse. . . . In want thereof, use the juyce of Limes, Oranges, or Citrons, or the pulp of Tamarinds.

It seems paradoxical but it was the very success of his investigations and the measures based thereon that led to Lind's work being almost forgotten. Scurvy was no longer a crying evil, medical interest in it passed and Lind was forgotten.

At first the lemon-juice supplied to the Navy was made from lemons grown in Spain and the Mediterranean countries. When Britain took over the West Indies the lime was used instead and scurvy again broke out, or rather cases increased in number. We now know the explanation of this, limes being poor in antiscorbutic vitamin as compared with lemons.

Another example of the benefits of lemon-juice on these long voyages is mentioned by G. Budd when speaking of the voyage of the *Suffolk* to Madras in 1840. In those days, at all events in this instance, the journey took nearly six months. Each member of the crew was given two-thirds of an ounce of lemon-juice daily. A few showed early symptoms of the disease which disappeared when the amount was increased. At that time the ration of lemon-juice in the Navy was 1 oz. daily with 1½ oz. of sugar started when the vessel had been at sea a fortnight.

It is interesting to note what Charles Curtis, a naval surgeon, wrote in 1807 on a discovery made by a Mr. Young who was connected with the Navy, but in what capacity I have not been able to ascertain :

. . . nothing more is necessary for the cure of this disease [scurvy] . . . than—not dead or dried but—fresh vegetable diet, greens or roots, in sufficient quantity. To be sure we cannot have a kitchen garden at sea, and a short and scanty crop of greens only can be raised on board ship ; but beans and pease and barley and other seeds brought under the malting or vegetating process are converted into the state of a growing plant, with the vital principle in full activity throughout the germ and pulp and if eaten in this state without any sort of preparation except that of separating or rejecting the husks, cannot fail to supply precisely what is wanted for the cure of scurvy. (Quoted from the *Medical Research Council Special Report Series*, No. 167. Vitamins, a Survey of Present Knowledge.)

The idea, however, was much older than either Mr. Young or Dr. Curtis knew. The good effects of fruit and vegetables obtained on reaching land by patients who were suffering from scurvy on a voyage led to the plan of laying out gardens at ports of call. Jacob van Heemskerck in 1598 laid out such a garden in Mauritius, where he called on his way to the Dutch East Indies and another on St. Helena where he was wont to call on the return voyage. He was not the only one ; we hear, for instance, of Wollebrand Geleynssen who had a garden and orchard at the Cape of

Good Hope in 1649, four years prior to van Riebeeck's arrival there.

Occasionally the vessels would not call at these ports or the voyage might take considerably longer than had been planned and the next step was the laying out of gardens actually on board. History relates that Hendrik Hagenaer did this on his ship, *Grol*, in 1631 and on the 18th March that year the first crop of cresses was served out to the sick and later on lettuce, radish, horse-radish and " some sort of scurvy grass." He was very unlucky for on 21st April a high sea washed the whole garden overboard and scurvy cases rapidly increased. By 28th May they numbered twenty-five, by 14th June fifty. The doctor was among those who succumbed and so many were ill that the remainder were too few to work the ship and handle the sails, so that on arrival at the Cape fresh men had to be brought from shore to help weigh the anchor.

In this connection it is interesting to note that Père Labat, writing of his travels among the West Indian islands in 1694, mentions that on board the ship one regular item on the daily menu was fresh salad grown in large boxes of earth. These, he says, were planted with wild chicory and were guarded day and night by a sentry for fear of damage being done to them by rats or sailors. " When one box was finished we sowed it with lettuce and radish seed, and had the pleasure of seeing this grow and then of eating it before we reached Martinique."

When Fürst in 1912 stated that he had found that dry cereals after soaking in water and being allowed to germinate became antiscorbutic, it was far from being, as was thought, a new discovery.

Vedder states that at the beginning of last century scurvy was common in the United States and he quotes Tapler, a surgeon, for the fact that in 1809 600 died from it in the Lower Mississippi and that in 1820 among a force (the strength is not given) sent to Council Bluffs more than 500 were attacked and 168 died. During the American Civil War 30,714 cases were recorded among the white troops and among the coloured many more.

We see from this that the disease was by no means confined to sailors ; mention has already been made of its prevalence among the besieged and among the French in the Crimean War, during the two years 1854–6, it is recorded that there were 23,250 cases of scurvy and 645 deaths from it among a complement of 86,740, and this leaves out of account many who died after setting out for home. Again, Hoff states that in the Russo-Japanese War

there were 1180 cases and ten deaths among the Russians—probably an underestimate. Finally, in the Great European War the Mesopotamian Field Force, especially the Indian contingent, suffered from the disease. According to the reports of Willcox, Hehir and Sheppard there were more than 11,000 cases among the European forces from faulty diet combined with hardship, and these were dealt with by provision of germinating beans and peas, cultivating vegetables in the occupied area, and the last-named showed the superiority of raw potatoes, as salad, to the fresh lime-juice from Bombay and the comparative uselessness of the ordinary West Indian lime-juice. In this war scurvy was present, says A. F. Hess (*Indian Journal of Public Health*), in the armies of all nationalities except the American, who were in the field for a short time only. Many cases escaped recognition under the diagnosis of " infective purpura."

In conclusion, infant scurvy was, at the beginning of the present century, reported to be very prevalent in the large cities of Australia and was ascribed to the increased use of artificial foods at an early age. The symptoms soon cleared up, without the aid of drugs, when a better balance and constitution of diet were made by the introduction of fresh orange-juice, raw beef-juice and unboiled milk.

II. POISONOUS FOODS

There are several fruits and vegetable substances used as food in the tropics which are nevertheless poisonous. Some are taken accidentally and should not be regarded as poisonous *foods*, such as the Manchineel Apple, or fruit of the *Hippomane mancinella*, the Physic Nut, fruit of *Jatropha curcas* and other species of Jatropha, varieties of Dioscoreaceae, or Wild Yam, varieties of Phaseolus, *Manihot utilissima*, the manioc or cassava, from which tapioca is prepared, the bitter variety of which contains cyanogenetic principles, and so on.

Apart from these there are fruits and vegetables used regularly as food and usually without any harmful results if due care is taken, but at other times with very fatal consequences. One only of these has a history, in that it was proved to be the cause of a disease which in certain years carried off more than 500 persons in one island of the West Indies, though the connection between the fruit and the disease was for decades unsuspected.

A second will also be referred to here, because, though the fruit itself is harmless, it proved for a time a puzzling cause of

poisoning, investigation showing that the toxic symptoms were due to an adulterant. The former of these two is Akee, the fruit of *Blighia sapida*, the second Jamaica Ginger.

A. AKEE POISONING

Akee is the name, in the native language of the Gold Coast, given to the tree *Blighia sapida* Koenig, and its fruit is Akyefufuo, as it is called in F. A. Irvine's *Plants of the Gold Coast*. It is described in books of the early nineteenth century dealing with Jamaican flora, *viz.*, *Sketches towards a Hortus Botanicus Americanus*, published in 1811, by W. J. Titford ; *Hortus Jamaicensis*, by J. Lunan, in 1814 ; the *Flora of Jamaica*, J. Macfadyen, 1837 ; and *A Naturalist's Sojourn in Jamaica*, by P. H. Gosse, 1851.

According to Jordan and Burrows the Akee was introduced into Jamaica by Dr. Thomas Clarke, the island botanist, in 1778 from a West African slave-ship. Koenig named it *Blighia sapida* in 1806, in honour of Bligh who brought the bread-fruit tree from the Pacific to Jamaica. It belongs to the same family as the horse-chestnut. The local name of the fruit on the West Coast of Africa is *isin* or *ishin*, and the fact that it might cause poisoning under certain conditions is evidenced by the old saying : " He who eats the ishin should know how to remove the poison." Cases are much rarer in West Africa than in the West Indies, and even in the latter cases of akee poisoning are practically confined to Jamaica. Though there have been vague surmises as regards the poisonous qualities of the fruit there were no definitely incriminating statements for more than a hundred years after its introduction to the West Indies.

In February 1886 a medical practitioner at the west end of the island of Jamaica wrote the following letter to the island chemist of the time, from which it will be seen that the danger of poisoning by the fruit was known :

MONTEGO BAY,
February 26th, 1886.

DEAR MR. BOWRY,

I have, with great interest, read your favour of the 25th inst., along with enclosed extract from a medical man, giving particulars of the deaths of several children in Vere [a district in Jamaica].

After a careful consideration of all the facts I cannot arrive at any other conclusion than [that] the cases there mentioned were those of narcotic poison, and the particular poison in this case, I feel confident, was that of the " Ackee," as the symptoms exactly tallies [*sic*] with my own experience of the poisonous action of the fruit.

If you will go to a little further trouble and have enquiries made, I think you will find that these children had been playing probably the day before under ackee trees, somewhere in the district, the probable inference is that they picked up portions of the decayed fruit and ate it. A great many times this condition of affairs have [sic] been brought to my notice; in the majority of cases I have not been able to prove that they did actually; but the history you always get is that they were playing under the tree and, more out of mischief, eat small portions of the decayed fruit that had been for some days on the ground. At a period of about 12 hours after[wards] the action of the poison commences, exactly as described in the extract from the letter you sent me, and always ends fatally. In my experience I have never seen a case of recovery, the prominent symptom being gradually increasing coma.

<div style="text-align:center">I will write again in a few days.</div>

<div style="text-align:right">Yours very truly,
ALEX. McCATTY.</div>

I have not been able to trace the original enclosed letter written by the medical man at Vere, where the cases occurred, nor the subsequent letter (if Dr. McCatty wrote again). The cases referred to were twelve in number, nine of the patients being under twelve years, one of thirteen, one of fourteen and one adult of twenty-nine years. History proved that all had eaten akees and the symptoms were vomiting, convulsions and coma ending in death.

Bowry carried out experiments and concluded that it was usually the fruits without well-formed seeds that were deadly. Not that fruits with abortive seeds are necessarily poisonous; when ripe and perfectly fresh, the author believes them to be as wholesome as those with perfect seeds, indeed by actual experiments he has found such akees to be wholesome. But these seedless fruits are apt to become over-ripe, stale and even decayed, without opening.

" It would appear," says Bowry, " that the decay which takes place in the unopened fruit results in rendering it deadly, as decay in open fruit does not."

Bowry obtained extracts from suspected akees and proved their toxicity on various animals, but never succeeded in obtaining the same poisonous extract from the viscera of a person poisoned by akee. In Bowry's own words : " There is no known method of recognizing poisonous ackees after they have been eaten [he means by chemical tests], even if any remain in the stomach after the vomiting." But if wholesome akees were allowed to remain till mouldy and rotten they did not yield a poisonous extract, indicating that it was not ordinary decay but some specific poison in the ' unwholesome ' akee.

Most of the victims were children, " probably because they are not acquainted with the conditions under which ackees are considered by adults to be dangerous, and so pick them unripe, off broken limbs and from the ground, and eat them with fatal results."

On the other hand it was thought that some deaths ascribed to akee were actually cases of cerebrospinal fever (the significance of this will be seen in the sequel).

Twenty-nine years passed ere this subject was again taken up scientifically and then in a quite different connection, as will be seen. In the meantime akee poisoning was noted in the Annual Reports of the Island Chemist as a cause of sickness and death, but not mentioned as a cause of death in the Annual Reports of the Medical Department until 1904 and not entered in the Registrar General's returns (except under the head of ' Food Poisoning ') until 1918.

We will now retrace our steps and approach the matter from a different angle. From the beginning of the present century a mysterious disease was reported which at times took on an epidemic character, caused many deaths, wiping out whole families in less than twenty-four hours, and giving rise in some districts to a veritable panic.

The earliest available records are those of Dr. R. G. S. Bell, of the May Pen district, of cases in January 1900, of Dr. H. G. Tillman in the Vere district in February of the same year, of Dr. Cooke in Mandeville, Dr. Thomson in Chapelton, Dr. R. S. Turton in Stony Hill, and others. It was prevalent between November and March and mostly from December to February. Briefly the symptoms were these : The patient, almost invariably a child, in apparent perfect health suddenly complains of feeling sick and ill and of abdominal discomfort, not, as a rule, pain. He then vomits, and this is repeated three or four times at short intervals, after which recovery seems to take place and, if it be daytime, the child returns to play ; if at night he drops off to sleep and all suspicion is lulled. Some three to four hours later the child wakes, if asleep, again complains of feeling sick and begins again to vomit ; but, whereas the initial vomiting is of an irritant character with effort, this second attack is effortless, of a pumping cerebral character, the vomitus being frothy mucus or watery fluid. Soon after, it may be a matter of a few minutes only, convulsions appear—but not invariably—coma rapidly supervenes and deepens till death in twelve hours or so from the first onset.

It will be readily understood how a state of panic would arise when one after another in a family would exhibit these symptoms and one house after another, or simultaneously, be attacked, and within twenty-four hours in a small village some twenty or more children who had been playing happily and in excellent health one day were lying dead the next. Experience of several hundred cases has convinced the writer that no patient exhibiting the secondary vomiting and the convulsions ever recovered. The disease was reported under the non-committal name of the *Vomiting Sickness*. The only post-mortem appearances were hyperæmia of the gastric mucosa, of meninges and kidneys, and possibly petechial spots in the stomach and the brain, ascribable to the strain of vomiting.

In 1904–05 Dr. Errington Ker, Head of the Medical Department of the Island, called special attention to the malady and recommended systematic investigation of it. The report for 1906 referred to its occurrence in various districts, and in 1907 note was made that it had been more prevalent than usual; in one district, Clarendon, eighty to ninety deaths from it were recorded and many more, certified under other names, such as infantile convulsions, meningitis, epilepsy, food-poisoning, and so on, were believed to have occurred. Each year there were cases, sometimes more, sometimes less, and in 1910 it was very severe, as the following table shows.

Parsh.	Month and Year.							Total.
	1908.	1909.				1910.		
	Dec.	Jan.	Feb.	Mar.	Dec.	Jan.	Feb.	
St. Andrew .	6	1	1	—	3	8	16	35
St. Catherine	9	4	3	2	22	10	1	51
Trelawny . .	15	38	13	7	7	12	9	101
Westmoreland	2	—	1	3	3	5	—	14
Clarendon .	42	14	14	7	91	43	19	230
St. Thomas .	—	1	—	—	4	8	1	14
Hanover . .	3	7	8	1	2	1	3	25
St. James .	4	20	15	1	10	3	4	57
Manchester .	7	13	3	3	47	19	1	93
	88	98	58	24	189	109	54	
	244				24	352		620

Dr. Ker, referring to the condition, says :

Many of these cases may be, and undoubtedly are, due to ackee poisoning, possibly cassava poisoning, worms, meningitis, bronchitis, gastritis, and other diseases, there is little doubt, but beyond these there remains an unexplained residue which needs explanation.

In 1911 outbreaks of 'vomiting sickness' were reported from Stony Hill, Claremont, St. Anne's Bay, Duncans, Falmouth, Montego Bay, Newport, Crofts Hill and Chapelton, and at the request of the Government Captain T. J. Potter, R.A.M.C., was sent out to investigate it.

When in 1904 and 1905 the disease began to attract special notice a letter was addressed to the authorities of other West Indian Islands describing the 'vomiting sickness' and asking whether any similar condition prevailed in them. Replies were received from Cuba, Haiti, Nassau, Trinidad, Grenada, Barbados, Dominica, Antigua, St. Lucia, St. Vincent, Porto Rico and British Guiana. All were negative, but two are of interest. One from Cuba, from Dr. Carlos Finlay of yellow-fever fame, who mentioned an outbreak in 1899 which he called cerebrospinal meningitis, with five fatal cases in an American regiment near Mariano. This was certainly not the same as the Jamaican vomiting sickness, for it did not recur and the symptoms were different (see later on the distinctions between vomiting sickness and cerebrospinal fever). The other was from the Consul General of Haiti who wrote :

There is a somewhat similar disease in this Island. It has not, however, proved to be particularly dangerous. It generally happens during the months of February, March and April, when there is a difference in temperature by day and by night. It can best be described as severé bowel troubles, together with high fever and vomiting. Europeans suffer principally from it, and natives to a much less extent. Children are apt to suffer from it, but there does not appear to be any high mortality from it. The attack (acute stage) lasts on an average from three to five days, when improvement sets in with rapid convalescence.

Clearly this bears little if any resemblance to the Vomiting Sickness of Jamaica ; the differences will be seen more readily from the tabulated statement on p. 944.

The disease, therefore, at least in epidemic form, was limited to Jamaica.

T. J. Potter arrived in Jamaica on Christmas Day 1910, and remained till August. His report was published in 1912 and he was of opinion that the majority of deaths ascribed to the so-called 'vomiting sickness' were due to yellow fever. This need

not be considered further; the length of illness, the high fatality among young children and the absence of black vomit are sufficient to exclude this.

Haitian Disease.	Vomiting Sickness.
1. Bowel troubles.	1. No bowel troubles as a rule.
2. High fever.	2. Rarely any fever; temperature may reach 99·4°, seldom 100° F.
3. Europeans principally attacked; natives less.	3. Europeans practically never; natives 99 per cent.
4. Fatality not high.	4. Fatality over 80 per cent.
5. Attack (acute stage) lasts 3–5 days.	5. Death usually in 12–15 hours, and may take place in less.

Next came a recrudescence of an old idea, spoken of above, that these patients were suffering from cerebrospinal meningitis and, as Scott showed, among those reported as dying of vomiting sickness, some were probably instances of cerebrospinal fever, for the symptoms might include headache, retraction of the neck, Kernig's sign, and a Gram-negative diplococcus could be at times isolated from the cerebrospinal fluid. On clinical grounds these cases differed in several important features from those with vomiting sickness. These differences may also be shown in tabular form.

Meningitis-like cases.	True Vomiting Sickness Cases.
1. May be catarrhal prodromata.	1. No prodromata; onset in the midst of health.
2. Headache present and severe.	2. No headache.
3. General tenderness and hyperæsthesia common.	3. No pain; may be abdominal discomfort.
4. Rigidity often present.	4. General limp condition between convulsions.
5. Retraction of head.	5. No head retraction.
6. Kernig's sign present.	6. Kernig's sign absent.
7. Consciousness returns between convulsions, or even retained during fits, if not severe.	7. No recovery, if consciousness once lost.
8. Course sometimes rapid, but may be prolonged.	8. Course rapid; death usually in 12–15 hours.
9. Recovery slow.	9. Recovery complete, if death not within 24 hours.
10. Fever present.	10. Little, usually no, rise in temperature.
11. Diplococci in cerebrospinal fluid.	11. Cerebrospinal fluid sterile.
12. Pus found in meninges at autopsy.	12. No pus found post mortem.

In December 1912 the Committee of the Liverpool School of Tropical Medicine sent out Dr. Harald Seidelin (probably in view of Potter's conclusions that the disease was yellow fever and of Seidelin's experience of this disease in Yucatán, Mexico), who arrived at Jamaica in January 1913 and left towards the end of March, having investigated sixty-two cases. His report was published in November 1913, and is particularly valuable for the accounts of the post-mortem findings, macroscopic and histological. He came to the conclusion that the condition was neither yellow fever nor meningitis, but arrived at no positive opinion except that in some cases a diplococcus, differing from the meningococcus of Weichselbaum, was to be found in the cerebrospinal fluid ; this organism he named *Diplococcus jamaicensis*.

Matters remained in this state of uncertainty when in February 1915 a very severe outbreak occurred in Montego Bay district and eighteen deaths took place in two days. H. H. Scott, as Government Pathologist, was sent to investigate and saw a large number of cases from start to finish and the sense of utter helplessness among the people in the face of such disaster was terribly distressing.

The symptoms of such as were seen in the early stages and followed through to recovery or to the fatal issue were typical, as have been described above. The post-mortem appearances were those recorded by Seidelin and subsequent examination of the tissues showed the accuracy of Seidelin's account of the morbid histological changes.

Epidemiological demands which any explanation would have to satisfy were the following :

1. The peculiar seasonal prevalence, November to March, and particularly December to February.

2. Limitation of the disease to Jamaica, so far as was known.

3. Sudden onset in apparent good health and in the well-nourished equally with the poor and underfed.

4. Rapid and complete recovery of non-fatal cases.

5. Attack of several in one house or close neighbours in a settlement.

6. The vastly greater preponderance in children.

7. No preference as regards sex.

8. Europeans and their children practically never attacked, and East Indians rarely.

Scott noticed that where the early vomit had been saved for inspection, among various articles eaten, one was invariably present

—fragments of akee—and this clue was followed up, Records for the preceding three or four years when analysed showed that the deaths from Vomiting Sickness took place in the main akee season, *i.e.* the cooler months when other fruits and natural foods were relatively scarce.

Next, akees, though growing in other West Indian islands, were few in number, were regarded as curiosities, and the fruit was not used as a regular article of food, and, as the reports from other islands referred to above showed, vomiting sickness was a disease confined to Jamaica. Thirdly, the sudden onset of symptoms when the subject was in good health pointed to food poisoning, especially when several of a household were attacked at or near the same time ; fourthly, the rapid and complete recovery of those who did not die might also be explained by food poisoning. Fifthly, the greater preponderance in children. This we may postpone for the moment as that was not obvious till after some experimental work had been carried out. Sixthly, no preference for sex ; this one would expect if the cause were some toxic food. Seventh, comparative absence of cases among Europeans and East Indians.

Following up this clue by experimental work Scott was able to show that akees when prepared in the usual way, as done by the natives, by boiling the arilli in water, were, if they were properly ripened and developed, innocuous. If they were unopened or taken from a broken limb or were immature, the water in which they were boiled became highly toxic to carnivorous laboratory animals, producing tissue changes indistinguishable from those in human akee-poisoning cases and cases of vomiting sickness as described by Seidelin and Scott. The fruit pulp itself, if then separated from the water, was usually harmless. Commonly the ' pot water ' or ' akee soup ' would be given to children who would thus drink the extracted poison, whereas the adult members of the family would eat the now harmless pulp ; thus would be explained the preponderance of children as victims. Children on their way to school, seeing a branch on the ground, perhaps blown down by a storm, would take the unopened, unripe fruit, eat it and be poisoned.

Again, the European rarely eats the akee unless it is gathered from his own trees and he chooses the ripe, mature and naturally opened fruit ; the East Indian coolie rarely eats it at all, and the paucity of cases among them has already been commented upon.

Scott concluded from his epidemiological investigations and experimental researches that akees under certain conditions are

poisonous and among such conditions are : (*i*) Unopened akees ; (*ii*) Akees plucked from a decayed, bruised or broken branch ; (*iii*) Akees which have not matured and opened naturally, but which have been forced open ; (*iv*) Akees with a soft spot in fruit in other respects apparently sound. Also that much of the poison is extracted by boiling with water.

His interpretation of the symptoms was that some poison is taken, or some substance which acts as a poison after it enters the stomach and causes vomiting by direct action. This comes on in two hours or so after the solid is taken, sooner if the ' pot water ' is drunk. If this ' initial vomiting ' is sufficient to get rid of the poisonous substance no further symptoms occur and recovery is rapid. If not, there is an interval, usually of two to four hours, a more or less quiescent period of absorption, after which there follow symptoms due to the action of the absorbed poison on the higher centres, *viz.* ' secondary ' (cerebral) vomiting, convulsions, drowsiness, coma and death.

A. Connal and W. Ralston in Nigeria repeated Scott's work, using the ' isin ' (v.s.) and were able to confirm the toxicity of the fruit.

Thus the two paths of investigation led to the one centre—akee poisoning on the one side and ' vomiting sickness ' on the other—and the two conditions were shown to be one and the same.

Matters remained in this state till 1937 when Edwin O. Jordan and William Burrows, of the Department of Hygiene and Bacteriology of the University of Chicago, restudied the whole question and published a most interesting article on their findings, entitled *The Vomiting Sickness of Jamaica, British West Indies, and its Relation to Akee Poisoning.* They showed the connection on epidemiological and experimental grounds, but carried the latter farther than Scott had done. Scott had shown that alcoholic extracts of the fruit were non-toxic whereas the watery extracts were highly toxic and he suggested the administration of alcohol —convenient in Jamaica in the form of rum—in the earliest stages of the vomiting whereby the poison, whatever it be, might be rendered inert and so forestall the secondary symptoms—secondary cerebral vomiting, convulsions and coma—arising from absorption of the poison and this remedy had resulted in the saving of many lives. Scott had also suggested, but purely as a guess, that as no toxin could be found in the stomach contents or tissues post mortem, the poison was a substance readily decomposed or changed so as to be unrecognizable by the usual tests, perhaps a glucoside. Jordan and Burrows carried things further,

testing the different parts of the fruit, estimating the toxicity of the various parts and determining the chemical properties of the poison and their experimental evidence favours the glucoside nature of the poison. Quite recently, in 1938, Leigh Evans and Arnold have adduced further experimental work indicating that the poison is probably a glucoside.

In conclusion, there is no doubt that under the term ' vomiting sickness ' in Jamaica more than one disease has been included and deaths from gastro-enteritis, cerebrospinal fever, cerebral and algid forms of malaria, and conditions associated with heavy helminthic infestations, and food poisoning have been loosely certified under this heading. But of these cerebrospinal fever and helminthic infestations do not kill in 12–24 hours and only a careless diagnostician could confuse them with the condition described above as Vomiting Sickness.

Another form of food poisoning known in the tropics, but not confined to Jamaica as is Akee poisoning, is that by manioc or cassava. There are two kinds of Manioc (a corruption of Manihot) —*Manihot aipi* or Sweet Cassava, and *M. utilissima* or Bitter Cassava. The former is used as a vegetable and is harmless ; from the latter are prepared starch, tapioca, cassava cakes and other products. This species is, consequently, more cultivated than the former. Poisoning by it results from failure to remove the contained glucoside and enzyme which in the presence of water react to set free hydrocyanic acid, in other words the milky juice is cyanogenetic. The bitter variety grows more rapidly than the sweet and its toxic properties are no new discovery. Livingstone mentioned that to get rid of the poison the natives would place it for four days in a pool of water, by which time it had become partially decomposed. It was then taken out, the skin stripped off and the tuber exposed to the sun, after which it was dried and pounded to a flour. In the West Indies it is usual to crush the tuber and wash it well three times, throwing away the wash-water each time.

At Angola another method was in vogue. There, if planted in a dry soil, it takes about two years to come to perfection. It bears drought well, not shrinking or shrivelling up like other plants. When planted in alluvial soils and well supplied with rain or flooded annually, it may come to maturity in a year. The root is rasped and then placed on a cloth and rubbed with the hands while water is poured upon it ; it thus parts with its starchy, glutinous constituents which settle at the bottom of the vessel, the water is poured off (this is important as it contains the poisonous

element) and the residue placed in the sun till nearly dry. The process is completed on an iron plate over a slow fire, the mass being stirred meanwhile with a stick, and, when quite dry, it is agglutinated in small globules—the tapioca of commerce. It is a cheap food because little labour is needed to cultivate it, and it is said never to be attacked by weevils. According to Livingstone, " throughout the interior parts of Angola, fine manioc meal, which could with ease have been converted into superior starch or tapioca, is commonly sold at the rate of about ten pounds for a penny."

In Jamaica, and in fact wherever the tuber is used for food, the natives are well aware of the risk of poisoning by it if it is not properly prepared ; hence cases of poisoning by it are rare.

B. GINGER PARALYSIS

Paralytic symptoms following the drinking of Jamaica Ginger, so-called, or ' Jake Paralysis,' were the result of a form of food poisoning with a much shorter history than that of Akee. It dates back no farther than 1930.

Early that year, February to April, attention was drawn to mysterious outbreaks of paralysis in certain parts of the United States of America, notably in Cincinnati and Tennessee ; male adults were chiefly attacked and all gave a history of drinking Jamaica ginger one and a half to three weeks before the onset. The most striking symptom was a flaccid paralysis of the distal muscles of the limbs. Three cases occurred in the United States army at Hot Springs. There was no involvement of the sensory nerves apart from a feeling of numbness and an aching of the calves preceding the actual paralysis by three or four days ; later the arms became involved ; the knee-jerks were increased, plantar reflexes abolished, and there was subjective loss of strength and objectively the flexor muscles were found to be weaker than the extensors. The patients had taken Jamaica ginger for years previously without ill effects.

In Oklahoma a case was seen at the end of February 1930, but by the 23rd April 536 cases were known and it has been estimated that there were some 1500 altogether. An outbreak occurred also in the middle and south-western States and in Southern California there were 125 cases. Three hundred and sixteen were admitted to the Cincinnati Hospital ; others were reported from Alabama, from Fort Benning, Georgia, from Ohio, Kansas, Kentucky, Mississippi and elsewhere. The condition was

common and widespread, becoming epidemic in several parts of America and it came to be known as "the 1930 type of poly-neuritis " or " polyneuritis of undetermined cause." To demon-strate how the cause was worked out the symptoms must be related in a little more detail. There was in some patients early gastro-intestinal disturbance, but in the majority the first symptoms were a sensation of cold, heaviness or soreness of the calves and two days later a weakness of the anterior tibial group of muscles set in leading to foot-drop and difficulty in walking. A common symptom was hyperhydrosis of the legs and feet with cyanosis, mottling and coldness. The weakness might extend to the thighs, but sphincter involvement was very rare. A week to ten days after the foot-drop came wrist-drop, but not as a rule complete, with wasting and reaction of degeneration in the thenar, hypo-thenar and interosseous muscles. No sensory nerve changes were detected and the tactile sense and that to pain and heat and cold were normal ; except for the tenderness of the calves there were no paræsthesiæ. The knee-jerks were present and might be exaggerated, but the Achilles and plantar reflexes were lost. There was no mental disturbance or affection of the cranial nerves—in short, the condition was an involvement of the peripheral nerves.

The severity might be gauged by the extent of upper limb involvement and recovery took place in an order the reverse of that of attack. Thus extensors of the forearm might recover some five months after onset of wrist-drop, the interossei on the ulnar side in 8–10 months and gradually those on the radial side and the thenar muscles. In the legs the thigh muscles would recover first but even in severe cases they were only partially affected.

Their condition was ascribed by the victims to their work, to the floors being damp and cold, to their working in draughts, and some States, Massachusetts was one, were at first in favour of awarding compensation, the idea being that the paralysis ought to be regarded as an industrial accident.

No changes could be found on blood examination ; the red and white cell counts were normal, there was no stippling of erythrocytes (important to look for in view of the possibility of lead palsy), no increase in reticulocytes or change in the sedimen-tation rate, and the Wassermann and Kahn reactions were negative. Death, if it occurred, was usually due to respiratory paralysis, and examination of nervous tissues revealed degeneration of the myelin sheaths and axis cylinders of the radial, ulnar, sciatic, external popliteal and anterior and posterior tibials, but not

extending up to the anterior roots ; one case was recorded as showing acute inflammation of a section of the cauda equina.

Further investigation resulted in an estimate that between 10,000 and 15,000 cases occurred in America and that the symptoms followed the use of an extract of Jamaica ginger. Children were never attacked and the average age of the victims was forty-seven years, men some seven to nine times as frequently as women. The fatality rate was not high, but the condition was of serious economic importance, for in some the disability persisted for two years and even longer.

Those attacked were moderate drinkers only of alcohol, and many had taken Jamaica ginger for years, but nevertheless this seemed to be common to all and was believed to be the cause or rather some adulterant of it, which was called provisionally ' adulterant X.'

The diagnosis attempted on clinical grounds was for some time in doubt. *Alcohol* as the cause of the neuritis was ruled out by the history and the absence of other symptoms—the mental symptoms of chronic alcoholism, Korsakoff's syndrome, etc. *Lead* palsy because of the rate of onset, absence of anæmia, colic, constipation, blue line on gums, stippling of red corpuscles and distribution of the paralysis. *Arsenic* was excluded because the symptoms differed from those of acute arsenic poisoning and there was none of the pigmentation or sensory symptoms of the chronic form. *Carbon monoxide, carbon bisulphide, phosphorus, mercury* or other metals were all considered but these rarely cause polyneuritis and then not of the purely motor type. *Beriberi* was ruled out by the absence of sensory symptoms, by the persistence of the knee-jerks, absence of œdema and cardiac symptoms ; *tabes* by absence of crises, presence of knee-jerks, absence of cranial nerve involvement, the negative Wassermann reaction and so on.

The credit for isolating the poison is due to Drs. M. I. Smith, E. Elvove, P. J. Valaer, W. M. Frazier and G. E. Mallory in Washington. They tracked the cause down to extract of Jamaica ginger. This was being sold in small bottles containing 2 oz. of the extract. As soon as the consignment came under suspicion many of those retailing it destroyed or threw away their stock, others denied having had any of it, hence the work of the investigators was hampered by the difficulty of obtaining samples. Finally Dr. Smith was able to prove that this consignment of the extract had been adulterated by the manufacturers and analysis showed that it contained 2 per cent. of triorthocresyl phosphate.

The discovery was further delayed by the peculiar resistance to the poison when it was tested on the usual small laboratory animals.

The symptom-complex as seen in man was reproduced only in certain animals and by certain methods of administration; calves and chickens, for example, reacted to it like human beings, other animals did not. Also the different cresyl phosphates set up quite different reactions; the toxic effect of triorthocresyl phosphate in rabbits was found to be three to five times as great as the corresponding ortho-, meta-, and paracresyl, and many times that of some of the esters closely related chemically.

Experiments carried out on rabbits proved unequivocally the delay in onset of symptoms according to the amount of the extract given. Thus, in doses of 1 gramme per kilo the animals sickened on the first day and died on the second; with 0·135 gramme they remained alive and well; with between 0·135 and 0·175 gramme per kilo they sickened in 10–11 days and died a few days later. The chemical action was found to consist in a union with the lipoid substances of the body and when this attained a certain concentration the function of the tissue was so impeded that symptoms appeared.

The peculiar selective action of the poison was shown by its having no effect on monkeys or dogs unless the material was broken down and fractionated, though, as just seen, it readily affected rabbits, and man occupied an intermediate position as regards susceptibility. To cause it to act in monkeys the tricresyl phosphate had to be saponified, heated, acidified and distilled, yielding phenols. After such treatment it set up the disease in monkeys receiving it by mouth.

Later experiments carried out at Tulane University, New Orleans, showed that the polyneuritis was distinct from that of beriberi or polyneuritis gallinarum. Chickens were given daily 2 c.c. of the fluid extract of ginger, and on the thirty-ninth day motor weakness was observed, with loss of co-ordination and the toes turned under when walking was attempted. Rice polishings were then given, but no improvement resulted. Similar experiments were undertaken when the outbreak of 'Jake paralysis' occurred at Oklahoma in 1930, control chickens being given unadulterated Jamaica ginger, while others were given the same with 1·5 per cent. of the phosphate. Symptoms appeared in the latter group only and almost uniformly nine days after this mixture was begun. The Southern California outbreak was traced to adulterated ginger which had been shipped from New York to Los Angeles in December.

In 1932 R. Carrillo and J. W. G. Ter Braak, in an article with the title *Estudio clinico, anatómico y experimental sobre un nuevo grupo de polineuritis: las polineuritis del fosfato de triortocresol* (ginger, *apiol y fosfato de creosota*), give a fairly complete description of the polyneuritis arising from apiol and Jamaica ginger poisoning. Apiol, it may be mentioned, is an alcoholic extract of the fruit of *Carum petroselinum*, the common parsley, which has for synonym *Apium petroselinum*. It is used as an abortifacient and contains from 28 to 50 per cent. triorthocresyl phosphoric acid. Its sale in drug-stores was prohibited in Germany in 1933.

Carrillo and Ter Braak showed the previous year, as already stated, that the toxic element of Apiol, of Jamaica ginger which caused the outbreaks, and of phosphate of creosote was the same. Also that the incubation period of the disease produced was about seventeen days, after which the paralysis set in abruptly and was followed by atrophy of muscles innervated by the sciatic ; that the nerve degeneration produced is not Wallerian but periaxial. They note that secondary cord changes occur, a fact at variance with the belief hitherto.

CHAPTER XX

THE SUEZ CANAL

The making of a canal through the Isthmus of Suez to link the Mediterranean with the Gulf of Suez and so with the Red Sea was no new project in the nineteenth century. Plutarch describes Cleopatra's "most bold and wonderful enterprise." Separating the modern Gulf of Suez from the Mediterranean was a belt of low-lying desert land, only thirty-five miles broad, and across the northern side of this the Pelusian branch of the Nile connected the Delta with the Mediterranean, the *mare internum* or *mare nostrum* of Cæsar. Farther to the south were the lakes of Balah and Timsah and between the latter and the Gulf of Suez the Bitter Lakes.

Nearly 500 years earlier Darius of Persia had joined these waters by a canal and sent his ships through, and even prior to him Rameses II had had a canal made between the Nile Delta and the Red Sea, but it soon filled up and fell into disuse. Darius' route differed but slightly from that of the modern Suez Canal. Darius' waterway silted up and King Ptolemy Philadelphus, 300 years later, reopened it and built a system of docks near the fortress of Clysma to the south. According to Aristotle, Strabo and Pliny, Sesostris built the canal and from an inscription on the temple of Karnack it was in existence in 1380 B.C. By silting and further sand deposits this also in time became blocked, in part at least, and transit of vessels from the Gulf to the Mediterranean could only be accomplished by dragging them for some miles over the desert land. In order to save her ships from capture by Octavian after the battle of Actium, Cleopatra had this carried out and supplemented her fleet by having vessels built at Suez. Her schemes, excellent in project, were frustrated by the Arabs from Petra and the district who were at enmity with the Egyptians and paid off old scores by raiding the docks and setting fire to the vessels under construction and also those which, at great labour, had been dragged overland from the Mediterranean.

Haroun-al-Raschid is said to have entertained the idea of a

canal in the eighth century A.D., but in fear of exposing the coast of Arabia to the attack of the Byzantine Navy he abandoned it. Seven centuries later the Venetians, who enjoyed most of the trade with the East by way of the Red Sea and Egypt, made overtures for the construction of a new canal, but when the Turks conquered Egypt the project fell through. Leibnitz in 1671, and Sheik Balad Ali a hundred years later (in 1770), were others who pondered on the question, but nothing of any moment was done until 1798 when Napoleon being in Egypt a survey was ordered and Lepère, the engineer, reported a difference of 29 feet between the level of the Red Sea and that of the Mediterranean.

We must not delay longer on ancient history which is beyond the scope of this work, since we have no medical details of interest relating to those times. Let us skip some eighteen centuries, to 1831. In that year the *Diogenes* sailed from Tunis and thirty-seven days later arrived at Alexandria where she was placed in quarantine. Among the passengers on board was Ferdinand de Lesseps. To relieve the tedium of quarantine the Consul, M. Minault, gave him a copy of Denon's Expedition to Egypt, and in this was the report of the engineer Lepère on the project of a canal at Suez. Lepère's study of the question was the outcome of an idea originating from Napoleon to connect the Red Sea with the Mediterranean by a waterway adequate for the passage of larger vessels. Lepère reported that the result of connecting them, owing to the difference of level, would be disastrous ; the project was consequently abandoned. De Lesseps, however, during the next seven years spent a good deal of time at Alexandria turning over the problem in his mind. The verdict of Lepère regarding the difference of level on the two sides of the Isthmus had been shown to be erroneous by the *Société d'Etudes pour le Canal de Suez* in 1847. This Society had been established by the Saint Simonist, Enfantino, as part of the socialistic programme for the regeneration of man. Another scheme of Saint Simon was a canal joining the Pacific with the Atlantic (Panama Canal). De Lesseps had been associated with this society and consequently had a strong interest in the idea of a Suez Canal.

At the same time an Englishman, Lieutenant Waghorn, was accustomed to visit Alexandria on his way to India and he tried more than once to convince the British Government that the route to India overland was preferable, being shorter, to that *viâ* the Cape. By this, the usual route, mails would take four to six months in transit. Waghorn, sure of his point, made journeys overland at his own cost and after much effort gained the doubtful

privilege of carrying duplicate despatches at his own expense. His route was *viâ* Marseilles or Trieste, thence on to Suez from Alexandria by camel or canal boat or, part of the way possibly by steamer, though he was rarely fortunate enough to obtain passage by the last. Like most pioneers he had little honour in his own country; in England he was, in short, regarded as a crank. He spent not only his resources but also his health in these attempts, which, however, proved most successful; so much so that the Bombay Government, in whose employ he was, was convinced of the advantages of his route. The crux of the matter, as they put it, was " Could steamers navigate the Red Sea ? " Admirals and politicians, the latter more vehemently than the former, protested that, though sailing vessels might be able to do so, steamers could not.

Lieutenant Waghorn's history is interesting and inspiring, but is wide of our present aim. Suffice it to say that he succeeded in establishing a route by which he was able to reach Alexandria the day after arriving at Suez, and by travelling from Alexandria by way of Trieste was in London twelve days from Suez—a remarkable achievement in 1845. Waghorn died in 1850 and as he had spent all his fortune on his efforts, his family would have been in sore straits but for the munificence of the Peninsular and Oriental Company who gave them a pension.

Between 1831 and 1838 de Lesseps, who was five years younger than Waghorn, used to meet the latter and discuss the project with him—in fact, as de Lesseps owned, Waghorn's steadfast fight against difficulty and opposition was an example for his own endeavours. At the age of twenty he was *attaché* to the French Consulate at Lisbon, and in succession after this at Tunis and Algiers and in 1831 held a similar position in Egypt. Here he made a study of the country and its people, cultivated their goodwill and became a friend of the ruler, Mehemet Ali, and his court —a piece of good fortune which was to prove of the utmost value later. His diplomatic duties subsequently took him to Rotterdam, Málaga and Barcelona in each of which he showed his abilities and reaped much honour. After twenty-nine years' service he resigned and went to live on his farm at Berry. Here he had leisure to think of other things than diplomacy and turned again to the study of Egypt and the East. He saw clearly that a canal across the Isthmus of Suez would increase enormously traffic to and from the East and in 1852 submitted a definite, thought-out plan to the authorities at Constantinople, but they rejected it on the grounds that the project was not within their sphere of action.

Two years later Abbas Pacha died and was succeeded by Said Pasha, the former Mehemet Ali. The latter greeted de Lesseps with enthusiasm, gave him one of his palaces for residence, and his hearty approval to the Canal project. The document which de Lesseps handed in gave a sketch of the projected canal and pointed out the advantages which would follow its accomplishment —an immense impulse to steam navigation, bringing into much closer contact countries along the Red Sea and the Persian Gulf, the eastern coast of Africa, India, Cochin-China, Japan, the Chinese Empire, the Philippines and Australia. Also, incidentally, it would prove, he said, an inexhaustible source of wealth for Egypt—a shrewd touch !

The concession was granted. The first step having been gained the next was to obtain money to enable a start to be made, and de Lesseps found a hundred friends and colleagues each of whom agreed to contribute £200. Twenty years afterwards each of these shares was worth £40,000, a two hundredfold increase. The sum so obtained was spent in studying the ground, estimating levels and so forth with the result that Lepère's statement of the great difference of level between the Red Sea and the Mediterranean was proved once again to be erroneous. These were now reported to be on the same level and there would, therefore, be no need to ' harness the Nile,' and construction of a canal joining them would be a simple matter, and Said Pasha expressed himself as willing to bear the whole cost. When matters had progressed so far England began to show hostility, and it appeared that the experience of Waghorn—stone-walling, if not active opposition— might be repeated. Great Britain's opposition was based on the plea that de Lesseps' project was nothing but a desire on the part of the French to interfere in the affairs of the East—an attitude analogous to that taken in 1551 by Britain in the matter of the Spanish Government and Panama.

De Lesseps started on a scheme of publicity ; he wrote to Richard Cobden pointing out that Great Britain had a very large empire in Asia, that something like half her general trade was with the Indies and China and that she ought not to need much convincing to see that the distance by the Suez route would be halved as compared with that round Africa viâ the Cape, and the trade costs greatly reduced. The reason brought against it was that shortening of the journey would mean reduction of the number of her merchantmen. De Lesseps replied that this argument was fallacious, for analogously the laying down of railways and shortening of journeys thereby had resulted in a huge increase

of business and traffic. Nonetheless, Great Britain persisted in her opposition and finally in 1858 the Universal Company of the Maritime Suez Canal was formed. Appeal was made for funds, £8,000,000 being asked for. France took more than half the shares, England and America took a few, the Khedive the remainder. The following year work was begun and twenty-five to thirty thousand men were at work.

A good account of the medical conditions is given in the reports of Dr. Aubert-Roche, the Chief Medical Officer to the undertaking, and that of Dr. Bougouin, the District Medical Officer (*Médecin de la circonscription*). The general conditions are thus described : The temperature at Port Said is lowest in January, average mean 15° C., highest in August, 27·6° ; inland 12·9° in January and 29·7° in July. Vegetation is poor, mere shrubs and thorny scrub mainly, with a few Caryophyllæ and varieties of sea-lavender. Marsh-formation, the cause of malaria and the chief reason of ill-health in most warm climates, is practically absent. The chief cause of sickness is the variation in temperature ; the air is often cold at night, and disease, such as it is (see below), is commonest between July and October, least from November to June, when diseases are mild and easily cured. The humidity is high and the Arab dwellings are exposed to the sun's rays by day and to the cold winds at night, with little protection. Their food is deficient, but they drink no alcohol. Their natural work is agricultural or on the canals, so that when employed on construction of the canal on the isthmus they are engaged practically in their normal occupation, hence their health was generally good ; moreover, they were well looked after. Many of them suffered from severe anæmia which was attributed to the defective diet ; it was evidently severe, for Dr. Bougouin states that many on examination had a venous bruit. Very likely it was the anæmia of hookworm infestation.

The report furnished in 1860 demonstrates the salubrity of the district and the playwork, one might call it, of the medical duties on the Canal scheme as compared with the later undertaking at Panama. The report deals *seriatim* with the various medical and sanitary establishments at important posts, namely, Port Said, Kantara, Ferdane, Guisr, Timsah, Toussoumville, Généffé, Alexandria and others. Of several of these the report states that " there has not been a single patient " and from the general summary we see that there were two hospitals, one at Port Said with four beds and one at Toussoum with seven ; at the latter and at Kantara there were ambulances. The health of the workers was

good : from the date of beginning the work in May 1859 to the date of this report, 25th June, 1860, there had been only four deaths, two from relapsed dysentery, one from cardiac aneurysm and one from acute nephritis, the former two only, it is said, being due to the locality and the climate. Sickness was at no time serious and was attributable mostly to the dust ; diarrhœa was troublesome in September and at various times ophthalmia prevailed.

In the medical report of 1862, when the work was in full swing, we find these words : Aucun travail de cette importance n'a été accompli dans des conditions sanitaires aussi satisfaisante (No work of such importance has been carried out under such satisfactory conditions).

Speaking of the diseases present, it is stated that ophthalmia is very common and is ascribed to a combination of four causes : first, change of temperature from the hot days to the cool nights ; second, to the sun's rays directly, or indirectly to the glare ; third, to the irritation of dust ; and lastly, " some unknown cause giving it its specificity." Europeans often are victims, the Arabs much less ; in the report for the nine months April 1861–January 1862 there were only eight cases recorded among 6000 Arabs. This is explained by Dr. Bougouin as being due to the fact that many are blind in one eye, the result of an attack in childhood, and the acquirement of immunity to subsequent infection thereby. *Hepatitis* and *Dysentery*—they are given in this order and no indication is to be found of any connection between them in the report—the former more severe, but the latter more common, predisposing causes being the climate and variations in temperature, direct causes excess or wrong food and the effect of alcohol. The latter applies to Europeans only, and especially to newcomers and the unacclimatized. Among the indigens there was only one case of hepatitis and five of dysentery in the period referred to. Diarrhœa and gastric disturbance were also fairly common and ascribed to the same causes and to the irritating dust. *Rheumatism* and *bronchitis* were also seen, but were not severe, and the latter yielded readily to treatment. *Pneumonia, phthisis* and *pleurisy* were practically absent. There was no ' pernicious fever ' ; only nine cases of *intermittent fever* mentioned in the table of disease among non-Europeans ; such malaria as does occur is ' very benign,' yielding readily to quinine sulphate and never showing relapses. *Typhus* was not seen at all. The medical personnel consisted of nine medical men and two apothecaries.

Certain figures of mortality are given which bear out the above.

In 1861–2 there were 1600 Europeans on the roll, at the Isthmus, at Damietta, Alexandria, Cairo and elsewhere. On the Isthmus itself about 1250, of whom 150 were women and children. Even including these there were only 20 deaths, or 1·6 per cent. Among the European workmen there were 13 deaths (1·18 per cent.) ; in the Army in France 2·23 per cent. Among the Arabs, out of 120,933 engaged in the work deaths numbered 23 or 0·019 per cent. The number of days lost through sickness was less than one-third that of the Army in France. The report adds that no disease was ascribable to the work, " the climate is salubrious, seasons regular and the sole danger—and that not a great one— the variations in temperature." Dr. Aubert-Roche adds : " Je ne puis, monsieur le Président, que vous affirmer la salubrité des travaux, la salubrité des localités, la salubrité du climat, en un mot, la salubrité de l'isthme, supérieure de beaucoup à cette de la France." And the report concludes with these words :

Son Altesse Saïd Pasha . . . n'expose à aucun danger la santé de ses sujets ; qu'il améliore dès à présent le sort de son peuple ; qu'il crée une source immense de richesse et de prospérité pour l'avenir de l'Europe ; et qu'enfin, en réunissant les deux mondes séparés depuis tant de siécles, il acquiert un titre de gloire qui rendra son nom à jamais ineffaçable aux yeux de la postérité.

Three years later it was attacked by disease from outside in the early months of the cholera outbreak which has gone by the name of the Fourth Pandemic of 1865–75 (see Cholera). It had started, as usual, in the Ganges basin, two years before. Indian pilgrims brought it to Mecca and in the panic that ensued it was carried in various directions, a vessel from Jedda arriving on 19th May brought pilgrims suffering from the disease to Suez.

The final report by Dr. Aubert-Roche in July 1869, besides giving the returns of the year ending 31st May, 1869, sums up the figures for the whole decade of the undertaking. In 1859 the population comprised 25 Europeans and 125 natives ; in 1869 there were 22,843 Europeans and 19,502 natives. Except for 1865–6, the cholera years, the mortality rates were consistently low, only once reaching 1·8 per cent. (in 1866–7) ; in 1859 it was 1·04 and in 1869 1·01 per cent., less than half that of France (2·4). In this last year the rate among European adults was 0·81 and infants 5·31 ; among the indigenous population 0·79 and 6·42 respectively, or men, women and children together 1·39 per cent. The infant mortality is ascribed to general conditions such as wrong feeding, diarrhœa, ' atmospheric influence,' inattention and

want of care in a climate differing from that whence their parents came—Malta, Italy, Greece. Among adults the chief causes of illness are given as ophthalmia, dysentery and diarrhœa, and hepatitis, and, less commonly, pneumonia. The direct cause assigned is the unwillingness of the workers to sleep in barracks ; they preferred to pass the night in the open and the fall in temperature being often as much as 10°, they might be chilled by sudden showers.

The length of the Canal from Port Said to the Gulf of Suez is a hundred miles and is a tide-level waterway without locks. The direction of the Isthmus is East and West (as also is that of Panama) and the Canal roughly North and South. On the Mediterranean side it crosses Lake Menzala, where the Canal is dredged and farther on, nearer the Gulf side, crosses the Bala, Timsah and Bitter Lakes. As we shall see later (see Panama Canal) the construction was comparatively simple as compared with that of Panama, and removal of material was easy. Cutting through the high ground of El Gisr, which rises 60 feet above sea-level, involved merely removal of loose sand with rock here and there. At first the Canal depth was to be 8 metres with a width at the base of 22 metres ; these were increased later to 9 metres deep and 25 bottom depths on the tangents between Port Said and the Bitter Lakes, 75 metres from there to Suez, 80 on the curves in order to facilitate the passing of ships.

At first the work was done by forced native labour, but on the disapproval of this by the British and Egyptian Governments, mechanical appliances and modern engineering methods were introduced. The work cost about double the original estimate.

The harsh desert of 1859 is now irrigated by the Sweet Water Canal ; groves of date-palms and acacia are scattered among cultivated lands along the shores of the Bitter Lakes. Corn, clover and cotton grow where, before, all was arid desert. Ismailia has its parks and flower-gardens.

17th November, 1869, was the day of inauguration, or the official opening of the Canal. The French steamer, *Aigle*, with the Empress Eugénie on board, went first and in her wake came the royal yachts of Austria, Prussia, Holland and Sweden, and a Russian man-of-war with Duke Michael on board. Forty vessels passed from Port Said to Ismailia.

Honours were showered upon de Lesseps, notably the Cross of the Legion of Honour by France, and he was made Honorary Knight Grand Commander of the Star of India by Her Majesty,

Queen Victoria, whose ministers had so strongly opposed the project.

For more than thirty years we hear nothing of the diseases of the Canal district, but in 1900 malaria was rife at Ismailia (see Malaria, p. 178) and Ross was sent by the Liverpool School of Tropical Medicine to investigate it. His findings, conclusions and recommendations have already been stated (see p. 178). At Suez itself malaria was also troublesome and. Ross in his search here also found no larvæ in the Canal or its channels, but many in the tanks connected with the works and in the small pools left in depressions in the drying mud.

CHAPTER XXI

THE PANAMA CANAL

It has been said that it was
either very careless or very astute of Nature to leave the entire length
of the American continent without a central passage from ocean to
ocean [from Atlantic to Pacific], or, having provided such a passage
at Nicaragua, to allow it to be obstructed again by volcanic action
(Saxon Mills).

In tertiary times, and probably later, the isthmus did not
exist as such, but the two oceans were connected by waterways
running between scattered islands. Geologically, the hills belong
to the Antilles system, not that of the Andes, and it is possible
that the Chagres River discharged its waters into the Pacific before
volcanic action raised the Culebra Hill.

We are told in historical works that Cortez at Darien gazed
with eagle eyes at the Pacific which he called the South Sea. In
the words of Keats's sonnet :

> And all his men
> Looked at each other with a wild surmise,
> Silent upon a peak in Darien.

There are two mistakes here which cannot be excused, the
first at least, by poetic licence. It was not Cortez but Nuñez de
Balboa who in 1513, on Michaelmas Day, was the first European
to see the Pacific from this side ; secondly, neither Balboa nor
anyone else could have viewed the Pacific from Darien. Having
sighted the Pacific Balboa waded into the water and took " real
and corporeal possession of the sea and its shores for the King
of Spain " and such is the irony of fate that now not a piece of
the territory extending for thousands of miles on either hand
belongs to Spain.

A man who had been with Balboa, a cousin of Cortez, by name
Alvaro de Saavedra Ceron, was the first to propose a waterway
through the isthmus. Galvano, the Portuguese historian, mentions
four possible routes : Darien, Panama, Nicaragua and Tehuan-
tepec, but states that Ceron prepared plans proposing a route

which is practically that of the present canal. Ceron, however, died and nothing came of his proposals.

Charles V of Spain was in favour of such a canal, but on his death his successor, Philip II, issued his veto of the project on the grounds that it would be impious to link together two great oceans which God had set asunder ; also he feared the growing power of England who might deprive him of the control of the canal if built, and he decreed death to anyone attempting to improve on the Panama-Bello route. This reminds one of Herodotus's story of the people of Cnidos who consulted the Delphic oracle regarding a canal through the isthmus : The Persians might come that way and attack them and " if Zeus had intended the place to be an island he would have made it one."

Before the geography of America was understood some passage was thought to exist and navigators tried in vain to find it, examining the coast of the continent, sailing up rivers—the St. Lawrence, Mississippi, River Plate—but discovering " no interoceanic passage throughout the length of two continents, stretching over 120° of latitude " (Reginald Enock). In 1521 Magellan discovered the strait which bears his name.

As the Spanish colonies of the Pacific coast developed, the Isthmus became one of the greatest trade routes of the world and vast treasure for the enrichment of the King of Spain was carried over the rough track by mules.

The attempted colonization of Darien and establishment of a trade route by Scotsmen is an episode belonging to the history of tropical medicine. The story has been told as follows : William Paterson was a clever but erratic economist born in 1658 in a Dumfriesshire farmhouse. He travelled to escape the religious persecution in Scotland at the time, wandered as a pedlar through England and thence crossed over to America occupying himself sometimes in preaching, at others in buccaneering ; as he put it, his longing to see strange lands led to his consorting with buccaneers (so called from ' buccan,' the smoke-dried meat in general use) and his intellectual and moral powers led to his being sought by them as their spiritual guide.

On his return from the Bahamas he tried to engage the interest of King James II in a scheme to establish a settlement on the Darien and so to " hold the key to the world's commerce." Neither the British, Dutch, nor German Governments would entertain the idea, so Paterson resolved to enter commerce, make a fortune and carry out his scheme himself. His was a versatile nature. In 1690 he was occupied in forming the Hampstead Water

Company. Four years later he formulated a bank scheme by which subscribers were to lend money to the natives, the debt becoming the bank stock. The Government was in need of money and adopted the scheme, thereby founding the Bank of England. Paterson became one of the directors.

At this time the East India Company controlled the trade of England with the Orient and, Scottish people being jealous, Paterson took his Darien scheme to Edinburgh where it gained rapid favour and in 1695 he obtained an Act of the Scottish parlia-ment for a Company with a capital of £600,000. This was at once over-subscribed, largely by ' interlopers ' in Scotland and London. An interloper was a term first applied at this period to unauthorized traders who tried to interfere with established trade monopolies. London subscriptions were cancelled by the jealous action of the East India Company. When the new Company was floated the Darien scheme became its main issue. A town was established at Darien and the name changed to New Edinburgh. The expedi-tion as a whole was, however, badly managed and, though Paterson had no share in this, there seemed to be an element of fraud in it. Quarrels arose in the Council, fever broke out and decimated the little colony, among the victims being Paterson's wife and children. Scotland, thinking that the undertaking was succeeding, collected subscriptions for further expeditions. The colony, however, was fated. The Spaniards attacked the settlement ; the survivors, weak from famine and fever, surrendered and left. Of the 2000 that came out from Scotland only a remnant survived and the Company failed, losing £300,000.

The Rev. Francis Borland, one of the chaplains to the expedi-tion, published in 1700 a book of *Memoirs*. In this he notes : " Here are also a great many troublesome insects, especially the country is full of ants, wood-lice and musketas." Further on, regarding the healthiness of the settlement, he says :

Our Countrymen who went thither first to settle, though for some time after their arrival these were pretty healthy, yet afterwards proved very sickly, and many of them died. Our People who went thither about a year after were generally very sickly through the whole time of their abode there, and it proved a grave to many of them, and that even in the dry and healthiest time of the year.

After being attacked and invested by the Spaniards the colonists suffered much from dysentery, and Borland writes : " So that it may be said of Darien : Thou Land devourest them and eatest up thy inhabitants. No wonder then that our Colonie neither did, nor could thrive there."

At the end of his *Memoirs* his lamentations drive him to attempt verse :

> No wonder then, our infant Colony
> In Darien could not long Time thriving be,
> By such ill Neighbours, in a Spot of Earth
> Beset with Griefs and daily views of Death.
> Remote from Friends, with Objects of Envy
> To many, who did wish we here might die.
> Our simple Strength, but feeble to support us,
> Our skill in such affairs, small to direct us,
> Besides an higher cause of our Distresses
> God's wrath against us for our great Trespasses.
> Then strange not that our new Plantation
> Soon died and came to Desolation.

For three-quarters of a century after the Darien attempt nothing further was done, but in 1771 the idea again came to the fore and at the instance of the Spanish Government a survey of the Tehuantepec isthmus was made, but this route was found impracticable and in 1778 another survey was made, this time of the Nicaragua route. Though two British agents who had accompanied the Commission reported that the project was possible the scheme was not carried further. Horatio Nelson, on his first active service, was sent to San Juan de Nicaragua in 1780 and was brought to death's door by fever. He reported favourably of the possibilities and stated that he would occupy Lake Nicaragua "the inland Gibraltar of Spanish America," the possession of which would command the pass between the two oceans and divide Spanish America into two. It was an unhealthy spot ; *190 out of 200 men comprising the crew of Nelson's ship are said to have died there.*

In 1808 the question of a Nicaragua Canal was again mooted, this time by Alexander von Humboldt ; concessions were applied for by Great Britain, the United States, France, Belgium and Holland, but nothing tangible resulted. Then for forty years we hear no more, till the discovery of gold in California and Oregon led to a rush from the United States and from Europe and there were calls for transport, easier and more rapid than the long and arduous journey across the Continent—there were no railways at that time—or the long and tempestuous voyage by Cape Horn. Many chose the shorter route from New York to Chagres, thence by native raft to Gorgona or Cruces, and on by the old Spanish road over the Culebra Pass to Panama. In the rainy season the short distance of forty miles might occupy seven or eight days, and many would fall by the wayside, victims of malaria, yellow fever, cholera, or the general hardships of hunger and fatigue.

The Americans in 1850 obtained a concession from the Government of Bogotá to build a railway and five years afterwards the first train traversed forest and swamp. Those who had been engaged in the construction suffered terribly.

The sufferings and death of the greater number of the eight hundred Chinese who were imported by the railway company as labourers on construction work, who embarked from their own country for the new land without any knowledge of the conditions which awaited them, are among the most terrible and pathetic in the history of Panama. It is stated that many committed suicide. Crowds of laborious peasantry from Ireland shared almost a similar fate ; and hordes of negroes followed. Races from all parts of the earth—Spain, Mongolia, Africa, Britain, India, and all else, of every kind of faith and language, were mixed together in this work, and their descendants today are shown in the extraordinarily mixed population of the isthmus. The region produced absolutely nothing of material, food, or resource, all of which came from New York.

So writes Reginald Enock in his history of the Panama Canal. The railway is said to have cost about £30,000 a mile, but so great was the traffic that it yielded a high dividend for some years, till in 1860 the Pacific Steam Navigation Company of London took passengers from Liverpool to the Pacific Coast.

A decade later the question of a waterway came more urgently to the fore and the United States Government sent out expeditions to examine into the feasibility of different routes, Darien, Panama and Nicaragua. Nine variants of the first were suggested, but two remained for final consideration, Panama and Nicaragua. The former had a length of thirty-five miles and a height of 300 feet had to be dealt with ; the latter 156 miles, the greatest height 150 feet, fifty miles covered by a lake 105 feet above sea-level, necessitating a lock canal. By the former route a tide level canal was thought possible.

As long before as 1827 Goethe in his Conversations with Eckermann had written :

It is absolutely indispensable for the United States to effect a way through from the Gulf of Mexico to the Pacific Ocean and I am certain they will compass it. This I should like to live to see, but I shall not . . . lastly, I should like to see the English in possession of a Suez Canal

—both wishes now *faits accomplis.*

The remarks of Trollope in 1860 with regard to Panama afford a good example of the dangers of prophecy. Panama, he said,

is a place whose glory has passed away. He considers at some length (*West Indies and the Spanish Main*) the question of a canal and mentions that projected canals across the isthmus have been many, noting the following :

1. A northerly one, selected by Cortez and pressed by him on the Spanish Government, passing through Mexico. From the Gulf of Camperhay, up the River Coatzacoalcoz to Tehuantepec. This was advocated as late as 1845, then abandoned.

2. From the head of the Lake of Dulce (Gulf of Honduras) through the State of Guatemala.

3. Several schemes for traversing the inland Lake of Nicaragua, mooted since the days of the Spanish occupation. The lake was to be reached either directly by the River San Juan or by entering this river from the ocean by the Colorado River.

4. The French Emperor's scheme of 1846—up the Lake of Nicaragua to its northern point, then entering the River Tipitapa, on to the northern Lake of Managua and to the Pacific at the port of Realejo.

5. Following practically the line of the Panama railway.

6. Over the isthmus of Darien ; thought feasible because it was the shortest.

7. Along the River Atrato into the Gulf of Darien. The river runs from the Andes parallel to the Pacific Coast and is navigable for many miles.

8. That advocated by M. Felix Belly, whom Trollope ridicules at length. In May 1858, he says, a convention was signed at Rivas in Nicaragua, but was ineffectual because the local presidents had no authority and Congress refused to ratify it. M. Belly then said that the French Government would become guarantor, though there is no documentary confirmation of this. But, says Trollope, even if all political obstacles were removed " the nature of the waters and land seem to prohibit the cutting of a canal " and the plan is too costly. A survey by Colonel Child, an engineer officer of the United States " proves the absolute absurdity of M. Belly's plan. He showed that a canal seventeen feet deep might be made, taking the course of the San Juan and that of the Lake, as suggested by M. Belly, for thirty-one million dollars. But such a depth would be valueless ; passengers, treasure and light goods are more easily transferred by the railway " and would also be quicker because there would be a delay of two days in the locks. " I cannot think," he adds, " that this new plan will ever be carried out " and " I cannot think that the project of which I have been speaking covers any true intention of making a canal." He goes even further and says, " I have a very strong opinion that such a canal will not and cannot be made."

The Panama Railway had been most costly, in great part because of the difficulty of obtaining the necessary labour. The natives would not work, Europeans died, and labourers had to be imported.

The difficulties certainly were formidable, as we shall see later.

In 1891 Dr. Nelson wrote concerning the seasons at Colon : " The wet season is from April to December when the people die of yellow fever in four to five days, and the dry or healthy season from December to April when they die of pernicious fever in twenty-four to thirty-six hours " (*Five Years at Panama*). We have already noted Anthony Froude's opinion of Panama (see Yellow Fever, p. 371). Another view, quoted by Johnson and recorded by Saxon Mills, is even more lugubrious :

A land as feverish to the imagination as to the body is Panama. It is a land making a fitting environment to the deeds of conspiracy, piracy, loot, cruelty and blood that have principally made its history for centuries. This gloomy, God-forsaken isthmus is a nightmare region. One descriptive writer has truly said of it that it is a land where the flowers have no odour, the birds no song ; where the men are without honour and the women without virtue. He is not far wrong. The birds brilliant as is their plumage, have no musical notes. The dense forests teem with bright-hued parrots, parroquets, and other birds which squeak and scream but do not sing. There are beautiful orchids to be found in the swamps and jungles—fair to look upon, but they have no odour . . . the reptiles and insects are often venomous, and myriads of parasites are ever ready to invade the human body and bring disease and death. In the atmosphere itself is something suggestive of the days of the old pirates and their fiendish cruelties and orgies. There is no life in the air ; it is depressing, damp, miasmatic and intensely hot. For a greater part of the year thunder showers succeed each other all day long and half the night, with sheet lightning all around the horizon after dark. There is practically no twilight, day passing almost instantly into night. It is no wonder that this uncanny land has made its residents degenerate into plotters, revolutionists, murderers, and thieves. Its aspect is one of darkness, treachery and curse.

It is obvious that de Lesseps had not the faintest conception of the difficulties with which he would be confronted in undertaking to construct a canal in Panama. Eulogy at the success of the Suez venture seems to have robbed him of all perspicacity. Do we see here an instance of the ὕβρις of the Greeks leading him on to his final catastrophe ? Renan in his speech at the election of de Lesseps to the French Academy said : " It was impossible, surely, that the generation which had tunnelled Mont Cenis and the St. Gothard should be deterred by a few sandbanks and lumps of rock at Suez, Corinth and Panama ! You were born to pierce isthmuses."

In short, the Suez Canal had been a complete success, now for Panama. The Suez Canal was sixty miles long, that of Panama would be less, fifty-four or so ; the shortest line ran in both cases north and south and both areas were till recently uninhabited

country—there were several points of similarity—but de Lesseps did not see why this should not be a similar triumphant success, not remembering that whereas the Suez Isthmus was a flat and sterile desert, Panama was hilly, with almost impenetrable jungle of tropical vegetation ; that Suez was healthy, Panama deadly. But he was now a man of over seventy years and, however energetic he may have been, he failed to realize the enormous difficulties of the new undertaking. The story of his failure, of the huge loss of life by disease, by earthquake, by tidal wave, of the colossal waste of men and money, of the political crises which resulted from the failure it is not for us to speak. What those difficulties were and the means by which they were surmounted are told in part in the pages dealing with Gorgas and yellow fever. In the present chapter a few more details will be given.

In 1876 there was founded in Paris the *Société Civile Internationale du Canal Interocéanique* and an expedition was despatched to examine the projected route and a concession was obtained from the Government of Colombia—the Wyse Concession, so-called from Lieutenant Wyse, the head of the expedition. In May 1879 a Congress of Delegates, 135 in number, from France, Great Britain, Germany and the United States, met in Paris. More than two-thirds were politicians and speculators and the rest were engineers or geographers. They passed a resolution in favour of the Panama route and a sea-level canal, and de Lesseps, who was seventy-three years of age, was declared on the strength of his Suez success, to be the right man to carry it out and he agreed to undertake it. De Lesseps was a man of despotic character and he refused to listen to those who opposed the idea of a sea-level canal on the grounds of the hydrographic condition of the Chagres River and excavation of the Culebra, and persisted in his views that plans which had succeeded at Suez should be followed at Panama.

Two years were spent in surveys and preliminary work and the outcome of these was that the construction would take eight years to complete and would cost 658 million francs. The scheme was for the canal to traverse low ground for six miles, from Colon to Gatun, then to pass up the Chagres Valley to Obispo, a distance of twenty-one miles, follow the Cumacho, a tributary of the Chagres, cut through the Culebra Pass, and then along the Valley of the Rio Grande to the Bay of Panama. This route ran almost parallel with the Panama railroad and was forty-seven miles in length. The railway having been previously granted a monopoly had

to be bought out, at a cost of twenty-five and a half million dollars.

On New Year's Day, 1880, de Lesseps' little daughter struck the first *coup de pioche* amid enthusiastic cheers and a gala performance took place at the Panama theatre with Sarah Bernhardt in the caste. We need not go into details ; according to the account generally accepted, the " management was characterized by a degree of extravagance and corruption rarely if ever equalled in the history of the world." If land was needed the owner asked and was awarded by the Colombian courts perhaps a thousand times its value and the French paid the price unquestioning. The expenditure in eight years amounted to 300 million dollars, or nearly four times that of the Suez Canal. Young engineers brought over from France worked in a fever-stricken jungle ; deaths from malaria and yellow fever were many, for at that time nothing was known of the cause or methods of prevention. The Director of Works was taken ill ; two engineers of repute came over from Paris and within a fortnight of their arrival were dead from the fever. Another man, renowned for his propagandist and journalistic powers, sent out by the promoters to report progress, fell a victim to yellow fever and died. In brief, at one period the death rate was as high as 176 per mille and frequently only one-fifth of the total complement was at work. It is not to be wondered at, in the face of these disasters, that the Company at the end of 1888 found itself bankrupt. De Lesseps became almost insane ; political capital was made of the dire result of the enterprise and scapegoats were needed. Ferdinand de Lesseps and his son Charles were among those prosecuted. In the end, though a member of the French Academy, a Fellow of many scientific societies, the Academy of Sciences among them—he had, as already mentioned (see Suez Canal), been awarded the Grand Cross of the Legion of Honour and been made an Honorary Knight Grand Commander of the Order of the Star of India—nevertheless he died poor in 1894.

The Americans had, quite naturally, never looked with favour on a Panama Canal controlled by Europeans and they proposed a rival project by the Nicaragua route. Work on this was started in 1889, but financial disturbances of the time resulted in stoppage of the work through bankruptcy of the Company. In 1895 Congress appointed a Board to consider the whole matter and furnish a report ; a second was appointed two years afterwards. Then came a revival of the Panama route and in 1899 there was

created an Isthmian Canal Commission, to some extent stimulated by the Spanish-American War of 1898. An American battleship, the *Oregon*, lying at San Francisco was ordered to proceed to Key West, Florida. By the only known route, round South America this meant a voyage of more than 13,000 miles. For a long interval no news of her was received and she was thought to have foundered or to have been captured. On her arrival there was a general cry of " Never again," the anxiety had been so great, and a demand for a canal under American control, not merely as a business undertaking, though that was not lost sight of, nor for renown, but as a measure of protection and development of her Pacific States.

Routes were re-examined and further comparison of the Panama and Nicaragua routes showed that the former would be shorter, would need fewer locks and less curving, and that, in point of time, whereas the latter would mean a passage of thirty-six hours or so, the former would take only a third of this. On the other hand the distance between New York and San Francisco was 377 miles less by the Nicaragua route and, moreover, it was not mixed up with any of the French concessions. Accordingly the American House of Representatives passed a Bill authorizing the Nicaragua Canal ; but this was amended by the Senate authorizing the President to acquire the French property at Panama, a New Panama Company having been organized ten years after the death of de Lesseps, under French auspices, of a semi-national character to carry out a scheme entailing two levels, an artificial lake by damming the Bohio reached by two locks, and another, also reached by two locks, supplied with water from a reservoir on the Upper Chagres.

The political side of the matter does not concern us ; discussion was long and at times waxed acrimonious as regards the Clayton-Bulwer Treaty of 1850, the Dickinson-Ayon Treaty of 1868, and the Hay-Pauncefort Treaty of 1901 on control, rights of way, and so forth, but these have no medical interest.

When the Americans had decided to start on the scheme in real earnest or, to use their own term, " to make the dirt fly," the residues of the French work were still to be seen—a melancholy lesson. Piles of rotting machinery were there, half buried in vegetation,

locomotives with trees growing out of them, houses falling to pieces . . . sections of railway tracks terminating in fever-haunted swamps. There were settlements along the line of the Panama Railroad, inhabited in some cases by the most extraordinary types of people—Negroes,

Chinamen, and derelicts of numerous nationalities, and the progeny created by their interbreeding, often inhabited shanties built on piles over stagnant fever-haunted pools. The old French Canal, from Colon to the Gatun Hills had become a stagnant ditch, but of what value it really was none knew. Malaria was everywhere present, the still more terrible menace of yellow fever hung over the zone, and the fearful visitor or traveller, almost loath to leave his steamer, hurried across the isthmus or slept in the hotels at Colon or Panama in dread (Enock).

To speak more particularly of the medical aspect. Though extravagance, maladministration and waste played a considerable part in bringing to naught the efforts of the French, the unhealthiness of the isthmus, in particular malaria and yellow fever, took an even greater share. No real attempts seem to have been made to cope with mosquito-borne disease systematically; we must, however, remember that much of our present knowledge of prevention of such infection dates subsequently to the time of which we are speaking, but even what was common knowledge then does not seem to have been applied. During their tenure of the isthmus 86,800 men were employed, an average of 10,850 per annum. Of the total, 52,814 were treated for illness and 5627 died; on the same computation an average of 6535 cases and 703 deaths annually. In September 1884 Enock records, the whole of the crew of a British brig died of yellow fever and there were 120 cases in Colon with a fatality rate of 66 per cent. and in that month the Canal Company buried 654 of its personnel. In spite of so appalling a morbidity and mortality the French company devoted only 0·5 per cent. of the total expenditure to hospital service, and to sanitation and general hygiene practically nothing.

In the early days of the American undertaking many lives were imperilled from delay in installing a water-supply and in obtaining mosquito-netting. This was due largely to the fact that the members of the Commission resided at Washington in comfort and knew little of the dangers and discomforts under which those on the spot lived and worked. This complacency was soon ended by President Roosevelt requiring the members to live on the isthmus. Engineers from the United States and Europe met and, by the plan finally adopted, the length of the waterway from the terminus at each end in deep water was fifty miles, including four and a half miles dredged in Limon Bay and five in Panama Bay, so the length from shore to shore would be forty and a half miles. The Gatun Lake, formed by erection of the dam, is twice the size of Lago Maggiore and only one-fifth less than that of Lake Geneva, occupying an area of about 164 square miles and trees; streams,

rocks, even whole villages were submerged and the Panama Railroad had to take a new course.

Another point should not be lost sight of and that is that though " this mighty trench through the isthmian hills is not only the biggest thing to the credit of a nation which delights in bigness, but the greatest achievement of its kind the world has ever seen," the Americans had not to start *de novo* ; two French companies had been engaged there for a score of years and much of their work could be adapted and utilized. At that time there were 700 West Indian negroes engaged in excavating the Culebra Cut. The rapid increase in personnel is revealed in the following figures : In December 1905 there were 5000 employees ; in 1906 24,000 ; in 1908 31,000 and in 1910 50,000, of whom one-seventh were White Americans, the same proportion Europeans, and five-sevenths West Indian negroes. The West Indian negro was found at first to be rather an inefficient worker ; this, however, was the result of insufficient or improper food. Arrangements were made whereby he was given good food and a properly balanced diet, the cost being wisely deducted from his wages, for on that account he ate all that was provided for him, and the consequence was a great improvement in his efficiency.

Native labourers—the Chinese form an exception—are never hard workers. " Working like a nigger " conveys a very different meaning to those who have had tropical experience from what it is intended to convey by those who have not, but in 1904 on the Panama Zone even the willing workers, and they were none too many, were incapable of hard physical toil. After the change of food and arrangements for his welfare had come into force, the negro became stronger and worked much better and in fact the British West Indian negro, who had been looked upon as ' weak and lazy,' rather than as incapable by reason of physical debility, became probably the most valuable section of labour in constructing the canal. In fact, the manner in which the Americans arranged and controlled the life of their employees in the Canal Zone stands every bit as much to their credit as the skill and perseverance in the engineering part of the undertaking. The system was ' Paternalism ' carried to its logical conclusions. The governing body provided its own catering and practically everything had to be imported. Offices, hotels, living quarters, hospitals, messes, kitchens, shops, storehouses were erected, laundry plants set up, cold storage established and the supply trains had refrigerator cars. There were proper labour camps, with Chinese and East Indian shops, canteens and restaurants.

In the centre of the village is the commissariat where the canal and railroad workers buy their food and clothing. . . . The commissariat does away with the middleman's profit and buys in such large quantity and for cash that it obtains the lowest prices (Saxon Mills).

Excavation of the Culebra Cut forms *sensu stricto* the ' canal ' ; much of the material removed was used in building the Gatun dam, some in filling in the Balboa swamp, some for breakwaters and embankments for the railway. There were several setbacks. A large landslide on 4th October, 1907, at Cucaracha caused the fear that the canal would never become an accomplished fact ; in 1910 the sides of the Cut " buckled in gravitation waves," in August 1912 and again the following year other land slides occurred, the last at Cucaracha again. On the 10th October, 1913, the final earth-barrier, the Gamboa Dyke, was demolished. This was done by President Wilson by electricity transmitted through Texas, Mexico, Tehuantepec, Nicaragua and Panama, a distance of more than 4000 miles, from the White House, Washington. ' Thus, a few days after the 400th anniversary of Balboa's first sight of the Great South Sea the waters of the Atlantic and Pacific mingled together. On the 20th November the French steamer *Louise,* which twenty-five years before had brought de Lesseps to Panama, was the first to traverse the isthmus by water—a gesture of the friendliest and a courtesy of the most polished on the part of America.

A mountain (the Culebra Pass) was removed and cast into the sea ; not by faith alone but by works also. Faith and self-confidence on the part of the engineers and medical staff, and the works of enormous and powerful steam shovels. The greatest liberty man has ever taken with nature (Bryce).

The Asswan Dam is based on granite on which is built masonry of natural stone ; the Gatun Dam is founded on the alluvial deposits of the Chagres River, on gravel firmly cemented with mud and clay to a depth of 280 feet before we come to solid rock and it was on the top of such alluvial deposits that the dam had to be constructed—a far more formidable undertaking than that of Asswan.

The length of the completed canal from deep water in Limon Bay to deep water at Panama is fifty miles of which only fifteen are at sea-level. The minimum width is 300 feet and minimum depth 41 feet. The highest point is 85 feet above sea-level at the water surface, and 45 feet at the level of the canal bottom, which along this stretch is 55 deep. The Suez Canal is 90 miles long, 108 feet in minimum width and 31 feet minimum depth ; the Kiel Canal is 61 miles long, with corresponding minima of 72 and

$29\frac{1}{2}$ feet. The Manchester Ship Canal is $35\frac{1}{2}$ miles long with minimum width of 120 feet and depth 26 feet. The Panama Canal is, therefore, not so long as that of Suez or Kiel, but is broader and deeper.[1]

The changes which the Panama Canal has effected in lengths of voyages and in sea-routes may be briefly stated. The subject is important because of the possible risk of conveyance of infection, in particular yellow fever, now that the communication between West and East is so reduced in time (for discussion of this see Yellow Fever).

Saxon Mills sums up these changes in the following words:

1. The canal reduces the distance between New York on the Eastern and all ports on the Western sea-board of America north of Panama by 8415 miles. The saving from New Orleans is much greater.

2. Liverpool is brought 6046 miles nearer to all ports on the western sea-board of America north of Panama (including, of course, Canada).

3. The saving between New York and the Pacific ports of America south of Panama depends, of course, on how far south these ports are. To Panama 8415, Puntas Arenas on the Straits of Magellan 1004 miles.

4. Liverpool is on an average about 2600 miles nearer to Pacific ports of America south of Panama—from 6046 at Panama itself to none between Puntas Arenas and Coronel.

5. All the Pacific ports of the Americas are, *viâ* Panama, 2759 miles nearer to New York than to Liverpool.

6. All Asia and Australia, but not New Zealand, will be nearer Europe by the Suez than by the Panama route.

7. New York is now nearer to Yokohama, Sydney and Melbourne than is Liverpool. Thus, Sydney was over 1500 miles nearer Liverpool (*viâ* Suez) than New York (*viâ* the Cape of Good Hope), but now is 2424 miles nearer New York (*viâ* Panama) than Liverpool (*viâ* Suez).

8. In brief, the Panama Canal cannot invade the main traffic field of the Suez route—the countries of Southern Asia, East Africa, the Red Sea and the Persian Gulf. The competitive region of the two canals lies east of Singapore.

In order to avoid interrupting the narrative of the history of the Panama Canal we have in the foregoing left on one side details of the medical aspect of this vast undertaking. Some of these have received mention in the chapter dealing with yellow fever and more will be said in the account of the life of Gorgas. Here they will be referred to in their special relation to the scheme for construction of the Canal.

We have mentioned above (p. 973) in general terms the morbidity among the workmen employed in the French undertaking.

[1] These figures and those which follow are taken from J. Saxon Mills' work *The Panama Canal*. Thos. Nelson & Sons, 1913.

They had erected good hospitals and these were well equipped for surgical cases and ordinary cases of sickness, but as in their day nothing was known as regards the mode of transmission of malaria and yellow fever, they did, they could do, nothing effectual by way of prophylaxis. The popular name bestowed on the fleecy clouds of the rainy season was " the White Death."

At the time when the Americans assumed charge of the Canal Zone it was probably the most malarious strip of territory in the whole world. Quite early in the two and a half years spent in the preliminary survey and preparation for the work the fact was borne in upon them that sanitation was the crucial, the essential factor, nay more, that without thorough, adequate sanitation the desired end could never be attained.

When, in 1904, Colonel W. C. Gorgas was appointed in charge of the Medical Department yellow fever was quiescent, as also was plague, and non-medical officials were inclined to regard the medical men as alarmists, and when the sanitary officers arrived in July they were coolly received and hampered rather than helped by the administrative officials. Then, in December of that year there were six cases of yellow fever, one fatal ; in January 1905 nineteen cases and eight deaths. Gorgas reported that " the experience of our predecessors was ample to convince us that unless we could protect our force against yellow fever and malaria we would be unable to accomplish the work." The local natives were, of course, most of them immune. In April there were nine cases, two deaths, among 300 non-immune employees ; in May thirty-three cases, eight fatal, and in June sixty-two cases altogether (thirty-four among the European employees) and nineteen deaths.

People were becoming frightened almost to the state of panic and homeward-bound steamers were crowded with refugee employees. A degree of confidence was restored, at a time when the outbreak was at its height, by the Governor of the Canal Zone, Charles E. Magoon, enforcing sanitary measures, having broken screening of buildings repaired and, in short, giving Gorgas his whole-hearted support. Workmen were taken temporarily from the canal construction and set on to sewers and waterworks. In June nineteen deaths from yellow fever had been reported (as already stated above). By 4th July a piped water-supply had been installed. In that month forty-two cases were notified, thirteen fatal ; in August twenty-seven cases, nine fatal. In December there was one case on the isthmus and one on the canal. Between October 1904 and September 1905 there were thirty-

seven fatal cases of yellow fever among 17,000 employees, and among the total population of the isthmus (employees and others) in the four months, May–August, there were forty-seven deaths from this disease and 108 from malaria.

In reality malaria was the more difficult question, the bigger problem, because the mosquito vector was not a domestic insect like that of yellow fever; moreover, a patient recovered from yellow fever attained a life-immunity from further attack and was no menace to his associates, whereas the malaria patient was always liable to further attacks and remained in many cases, if not in most, a permanent reservoir of infection. Gorgas applied the lessons he had learned from the Havana campaign. In April 1905, there were 4100 men of the Sanitation Department employed in mosquito extermination alone. As already mentioned, a new water-supply—a piped supply—was installed, whereby domestic receptacles were abolished; ruts and inequalities in the streets of Panama and Colon were filled in, pavements were constructed —in short, all the usual anti-mosquito measures were utilized, jungle clearing, soil drainage, oiling of ditches and puddles (with a mixture of crude carbolic acid, resin and caustic soda) and so forth. These were under the charge and supervision of the 'Anopheles Brigade' and in addition there was a 'Stegomyia Brigade' to deal with domestic mosquitoes and house to house inspection, as has been recorded in the chapter on Yellow Fever.

So much for the mosquito side of the problem. On the human side all patients suffering with fever were either removed to special buildings screened to exclude mosquitoes or, if permitted to remain in their own homes, had to live in houses whose doors and windows were furnished with fine copper-gauze screening. The first European labourers brought over had been quartered in unscreened buildings and one-third of them suffered from malaria; taught by this the authorities had screening fitted to the quarters assigned to the second batch and only 4 per cent. of these were attacked.

To deal with malaria, therefore, the sanitary squads cleared the jungle for a radius of a few hundred yards round the settlements, swampy areas and large pools were drained and smaller collections of water were oiled and quinine was freely used both for treatment and for prophylaxis. A few figures will demonstrate the results of these efforts.

In 1906 there was a working force of 26,000 and among them there were 21,739 cases of malaria (83·6 per cent.) admitted to hospitals and the death rate from malaria was 8 per mille among

the native workmen, 2 per mille among the whites. The following year the labour force numbered 39,000 and among them malaria admissions totalled 16,750 or 42·9 per cent., and the negro mortality rate fell to half, 4 per mille. Four years later, in the period July 1911–June 1912, there were 40,000 employees, but cases of malaria were less than one-third the number in 1906, *viz*. 7000 and deaths only 32 ; of these 22 were whites, and among the Americans living in screened quarters the death-rate was only 3·9 per mille. At that time the death-rate of London was 15, of Paris 17, and of New York 18 per mille—the death rate in the " most pestiferous district in the world " was one-fourth that of London and a little less than one-fifth that of the Americans in New York.

In the eight years of the undertaking, 1904–12, there were altogether 5141 deaths, 284 being Americans, and of the total 1022 died of violence or accident and 4119 of disease. This may seem high to those unacquainted with the Panama Zone, but is in marked contrast with the returns of the French scheme, amongst whom there was a loss of 50,000 in nine years, the chief causes being malaria and yellow fever. The small proportion of the total cost, which the French allocated to medical and sanitary work has been noted. In the case of the American undertaking the expenses of the Sanitary Department were 5 per cent. of the whole or proportionately tenfold that of the French.

Construction of the Panama Canal was brought to a successful issue, as we have seen, by the surmounting of many obstacles, the solving of many problems, chiefly medical. The story, to be complete, comprises, however, more than this. Conditions, it is true, were changed, but the Canal construction created new problems and in particular problems in connection with malaria. Samuel Darling in 1910 showed that eight species of Anopheles were known in Panama—three others were listed, namely, *A. gorgasi*, *A. malefactor* and *A. franciscanus*, but they have been proved since to be *tarsimaculatus*, *punctimacula* and *pseudopunctipennis* respectively—but that the chief vector was *A. albimanus*.

Rozeboom, studying the question again recently (1938), finds that there are now seventeen species, though fortunately most are not important as transmitters of malaria. Four recently discovered are potentially dangerous, namely, *A. albitarsis* which, in contrast with the Brazilian *albitarsis*, proved experimentally somewhat refractory to infection with the local strains of *P. falciparum* ; *A. bachmanni* which is infectible with human malaria but is markedly zoophilic and in consequence relatively harmless to man ; *A. strodei* which does not feed readily on man, and *A.*

oswaldoi which is not present in large numbers in populated, but only in unpopulated districts, and is therefore not of importance as a vector for man.

All this constitutes a warning ; *A. albimanus* remains the really dangerous vector of human malaria, but fresh potential vectors are entering on the scene.

The following important dates in the history of the Panama Zone and the Canal (extracted from Saxon Mills' work referred to above) may fitly conclude this chapter.

1497 Bay of Limon discovered by Columbus.
1500 Rodrigo de Bastidas, Balboa and La Cosa reached the isthmus near Porto Bello.
1513 Balboa left Coibo on the Gulf of Darien, 6th September, and sighted the Pacific Ocean on the 25th.
1519 The town of Panama founded by Pedrasias.
1520 Magellan discovered the Straits named after him.
1522 Gonzales de Avila discovered Lake Nicaragua.
1532 Search for Strait in the isthmus abandoned.
1550 Permanent roadway across the isthmus from Panama to Porto Bello used by Spanish treasure convoys.
1551 Gomara's appeal to King Charles V of Spain to construct a canal. Well received but frustrated by Charles's death and Philip II's veto.
1616 Survey for a Darien Canal ordered by Philip III.
1698 Paterson established a town at Darien and called it New Edinburgh.
1700 Failure of Paterson's venture and evacuation of Darien.
1771 Survey of Tehuantepec and Nicaragua by the Spaniards.
1779 Second survey by the Spaniards.
1825 United States asked by the Central American envoy to co-operate in constructing a canal.
1829 The Dutch obtained a concession from the Nicaraguan Government, but
1830 Revolution in the Netherlands and abandonment of the concession.
1855 Panama railway opened to traffic.
1869 President Grant appointed the Inter-oceanic Canal Commission to investigate four proposed routes.
        Suez Canal opened, 17th November.
1875 Grant's Commission reported in favour of the Nicaraguan route.
1876 Founding of La Société Civile Internationale du Canal Interocéanique, and Lieutenant Wyse obtained a concession from the Colombian Government.
1878 International Engineering Congress summoned at Paris, at instigation of de Lesseps.
1880 Compagnie Universelle du Canal Interocéanique de Panama formed and work started in February.
1887 America sends surveying party to Nicaragua.
1888 Maritime Canal Company established.

1889　French company bankrupt ; about two-fifths of the Canal done. New Panama Company formed.

1893　American project at Nicaragua abandoned because of trade depression.

1894　Death of Ferdinand de Lesseps.

1900　Report of Third Commission, December, deciding on the Nicaragua route.　Supplementary report recommending the Panama route and purchase of the French property.

1904　America occupies the isthmus.

1906　January.　Board decide in favour of sea-level scheme ; but since a lock-canal would be cheaper and quicker a high-level canal was decided upon finally.

1914　Completion of the Canal.

1915　Formal opening of the Canal on 20th November.

CHAPTER XXII

THE SLAVE-TRADE AND DISEASE

To describe the general conditions under which the trade in slaves was carried on in the sixteenth to nineteenth centuries would be beyond the projected scope of the present work. Our concern is with the traffic in so far as it conduced to and fostered the spread of disease among the captives and from them to those engaged in the trade and those for whom they laboured.

A great number of the negro inhabitants of Africa have existed and continued to exist from the earliest period of their history in a state of subjection and slavery and their children were born to the same inheritance. It must be understood at the outset that in Africa there were at least two classes of slaves—domestic slaves, and purchased slaves, some being born slaves, others born free but becoming slaves later. The lot of the domestic slave was not a hard one ; the master's authority did not extend beyond reasonable correction, and he could not sell his slave without first bringing him up for public trial. Purchased slaves came into a totally different category ; they were looked upon as 'foreigners' and had no legal protection, might be treated with severity and sold at the whim of the owner. Sometimes they had been collected in the course of, or as a result of, petty inter-tribal wars, but more were brought down in large caravans from the interior and of these some were slaves from birth, being born of enslaved mothers, others were free-born but became slaves, it might be by capture, or voluntarily in times of famine, or as a consequence of insolvency—a sort of voluntary liquidation—to work off a debt, or for punishment for crime such as murder, adultery, witchcraft. In times of famine it was not unusual for a man to ask 'to be put upon the slave-chain' to save himself from perishing of hunger, and those with large families might sell one or more of their children to purchase provisions for the others. Some of these would remain slaves and children born of slave parents were also slaves ; others might obtain their freedom and

hire themselves for work as servants or free labourers for a term of years. Their lot was often worse than their former condition of slavery, for at the end of the period of indenture the man had to be released or re-hired and consequently they were exploited and worked out in their first term.

A common way of obtaining slaves was for chiefs to arrange to raid each other and so obtain labour by making slaves of the subjects of the other or else a war was fostered in the manner described below. An account of the raiding procedure is given in the Report from the Select Committee on the Slave Trade, East Coast of Africa, 1871, quoted by W. Law Mathieson (*Great Britain and the Slave Trade*, 1839–1865). The slave dealer goes into the country with so many muskets and so many pieces of calico and he finds out the most powerful chief, gives him spirits and keeps him in a state of semi-drunkenness and tells him he must have more slaves ; he gives the chief muskets and powder on account and the latter immediately finds an opportunity to settle some old outstanding quarrel with some other chief and a war breaks out. Favourable conditions are thus created for carrying on the trade because famine is sure to follow in a country where the people are dependent on one wet season for tilling the ground ; it is only during the wet season that corn can be sown. Then a chief without food or without the means of buying food will sell off his people very cheaply indeed. Captures are made in war, kidnapping is prevalent, leading in turn to all sorts of petty disputes and retaliation and the more disturbed the country the cheaper the slaves become. Slaves obtained by one chief from another often settled on the land and paid rent in kind—rice, fowls, palm-oil—and in a few years regained their freedom as members of the tribe.

In the early days, and probably at all times, it was the peaceable negroes that became slaves, the militant tribes were left alone as capture and transportation of such would be a troublesome undertaking. Physically, the negro—the enslaved negro—was strong, docile and cheerful and, if fed, happy.

Slavery dates back to the dawn of history ; in early dynastic times slaves were imported into Lower Egypt, and they were employed in Carthage and in Rome, but until the Mohammedan conquest of Africa they were not brought in on a large scale. Thereafter they were imported from the Sudan, Abyssinia and the Zanzibar coast into Northern Africa, Arabia, Turkey and Persia. There can be no denying, however, that the great impetus to the trade came from Europe. The natives indigenous to America

were too few or too weak and indolent for compulsory agricultural work and in 1503 Africans were brought over to Hispaniola by the Spaniards to work in the mines, and ere long they were imported also into Mexico, Peru and Panama. In 1517 Charles V of Spain gave a Flemish merchant the exclusive privilege of importing 4000 slaves a year into America (H. Johnston). Later, some Genoese merchants bargained with the Portuguese Government for a supply of slaves from Guinea.

About the middle of the sixteenth century the British went out to Africa to investigate the trade in spices, but soon decided that traffic in slaves would be much more profitable and in 1562 Sir Richard Hawkins took his first cargo of slaves under the British flag to the West Indies and in 1564 and 1567 carried 800 purchased or captured negroes thither from the West Coast of Africa, and when Britain came into possession of Jamaica and other West Indian islands and began to develop the tobacco plantations of Virginia the need for labour became greater and England led the world in slave dealing. Hawkins soon found an easier and cheaper way of obtaining slaves by piratically attacking Portuguese ships and depriving them of their human cargo.

There is no glossing the fact that however much we, as Britons, pride ourselves on the part we played in abolition, in the early days, in the seventeenth and eighteenth centuries, we were as bad as any and worse than most. Between 1680 and 1786 there were imported into the British-American colonies 2,130,000 slaves and Jamaica alone in eighty years took 610,000 ; in the latter part of the eighteenth century European powers imported an average of over 70,000 negro slaves annually, Britain bringing at least half. At first they came from the Gambia, Sierra Leone and the Gold Coast ; later from Dahomé, Benin, Angola and Zambesi.

We have stated that in general the slave received humane treatment in his own country, but at the death of a chief their fate might be a hard one. Lovett Cameron records the burial of a chief of Urna. He states that on this occasion the course of a stream was diverted and in the bed was dug an enormous pit, and the bottom was lined with living women. At one end a woman on hands and knees supported the dead chief on her back, one of his wives being at each side while his second wife sat at his feet. Earth was then shovelled in and the women were all buried alive except the second wife who was killed before the grave was filled in. Next, some forty to fifty slaves were slaughtered (less for smaller chiefs) and their blood poured over the grave, after which the river was allowed to resume its course.

Slaves and ivory ranked equally in value as exports, beeswax and india-rubber considerably less. At that time, too, the whole trade of tropical Africa depended for transport on human beings as beasts of burden and when the slave trade was flourishing the carriers bringing the ivory to the coast were often sold also to add to the ivory-traders' gain. Between Bihé and Urna and Katanga, lines then occupied by the Portuguese, the slaves captured were taken not to the coast but inland and exchanged for ivory. Some traders are said to have " invoiced their slaves as bales of goods " and had a hundred baptized in a batch by the Bishop of Luanda, by aspersion, in order to save export duty.

The loss in numbers captured was but a proportion of the hardship and devastation inflicted in the course of capture. One author (Cameron) records coming upon a series of villages after an Arab raid. To procure 5000 slaves six times as many had been slain or had died by the roadside and over a hundred villages had been devastated. Many died of injury, starvation, cruelty and disease in the jungle ; sometimes, Cameron tells us, he would come across patches of corn denoting the haunts of fugitives from the slave-hunters, in flight also from natives of stronger villages who would hunt them down and exchange them for food from traders from Ujiji. The price of a slave was 4–6 doti or two goats, whereas at Ujiji, Lake Tanganyika, they were worth 20 doti ; the profits must have been enormous. Slaves were the chief medium of exchange and Cameron was for long held up and unable to obtain canoes because he had no slaves with which to pay for them.

The casual slave was usually caught, surprised in the woods a short distance from the village and was kept in chains to prevent escape. Often they were fairly well fed and not overloaded, but if there were many and the owners had themselves been slaves their treatment on the journey to the coast might be very cruel. Often they were gagged by a piece of wood like a snaffle tied in their mouths ; heavy slave-forks were placed at their necks and their hands were fastened behind their backs and were then attached by a cord to the vendor's waist. They were better treated when bought by traders than when in the hands of their native owners. In Cameron's day it was said that the slave-trade in Africa ' at a low estimate ' caused a loss of over half a million lives annually.

Even in the last quarter of the nineteenth century slavery existed in the Congo as bad as it had done in the preceding centuries. In 1876 Leopold of Belgium, a philanthropist whose aim was to realize Livingstone's ideals and regenerate negro Africa, obtained

on the strength of his assurances permission to levy import duties and through his agents enforced tribute from the natives in ivory and rubber, till they were reduced to a state worse than in the days of slavery. Those who have read Sir Roger Casement's report on the Congo (and later on Putumayo) need no reminder and those who have not need not be harassed by narration of the cruelties and mutilations inflicted on defaulters. Suffice it to say that the population was in fifteen years reduced from twenty millions to about nine millions. Another whose name should be remembered in honour in connection with the disclosures is E. D. Morel, a shipping clerk sent to Antwerp and elsewhere in Belgium because of his ability to speak French. In the course of his work he became acquainted with some of the facts and as a consequence of drawing his employers' attention to them he was dismissed and had to face insults and calumny from a subsidized press. He continued his efforts—a mere David fighting Goliath—till he roused public opinion in Britain, Belgium, Switzerland, France, Germany and the United States, and Roger Casement of the British Consular Service was sent to investigate. The result, given in his report, is well known. The policy of Leopold's successor differed vastly. King Albert visited the Congo Territory in 1907, traversing Congoland from Katanga to the mouth of the river, and free trade and freedom for the natives resulted.

Returning, in our historical account, to the West Coast. It was the need of Spain for labourers for her South American possessions in 1778 that caused her to become interested in the slave-trade in West Africa and she obtained from Portugal cession of the island of Fernando Po and made a settlement also at Cirisco Bay, on the coast of the Cameroons. The Dutch supplanted the Portuguese on the Gold Coast and an enormous increase of the trade in slaves followed. A large proportion of the negroes in the United States, Guiana and the West Indies were of Ashanti (Coromanti) and Fanti descent, and Dutch half-castes endure still on the Gold Coast. When the Dutch settled at Cape Town white labour was expensive and not very subservient. Native labour introduced from Angola and Mozambique was not found very efficient and others were brought from Madagascar and the Malay Archipelago. Thus the Cape became a slave-worked colony, but the slaves were treated kindly and their children received education.

Gold and silver were found in Mozambique in the seventeenth century, but the slave-trade proved even more profitable and in 1645 the first importation from there to Brazil took place owing

to the supply from Angola having come to an end during the time the Dutch were in possession.

The profit was said to be great in spite of the heavy mortality among the captives ; a general rough calculation stated that of the total captured, one-third would perish on the journey from the interior to the coast, another third in the Barracoons where they were collected for transportation, and less than a third lived to work on the plantations.

The first cargo of slaves to be landed in the Northern States of America was brought by the Dutch in August 1619 ; the first ship specially fitted up for slave traffic in America was the *Treasurer* of Virginia, and the first actually built in the United States for the specific purpose of the traffic was the *Desire* in 1636. Early in the eighteenth century Royal Companies were formed, treaties were signed and " the British slave-trade became a powerful institution " (Shufeldt). In 1770 there were 150 vessels belonging to Rhode Island alone engaged in the trade. Newport, it is said, was built almost entirely on slave-trade profits. The few figures given below will serve to show how rapid was the growth of the trade with individual colonies and these are not believed to be exceptional. In Virginia in 1700 there were 12,000 slaves ; sixty years later 150,000. In 1734 there were in South Carolina 22,000 slaves and only 8000 whites, and in 1850 the State of Louisiana alone had 244,985 slaves. Jamaica in one year, 1708, imported more than 6000 and in the five-year period 1725–30 between ten and eleven thousand. The population of the island in 1763 was stated to be 7768 whites, 9904 negroes ; in 1791 the relative figures were 30,000 and 250,000, exclusive of 10,000 free negroes and 1400 maroons. The whites being in such a minority there lurked a haunting dread of negro revolt under the gay surface of colonial life, and this fear was probably the greatest factor in the recorded instances of harsh and cruel treatment of the slaves.

In Barbados in 1628, before the introduction of slaves, there were 1400 whites ; in 1643 there were 6000 blacks ; in 1655 whites numbered 23,000 and blacks 20,000 ; thirteen years later the blacks were twice the whites in number, 40,000 and 20,000 respectively. In 1809, two years after abolition, the blacks outnumbered the whites by more than four to one, the figures being 69,119 and 15,566 respectively. In the decade 1698–1708 Barbados imported 35,409 slaves.

Distinction was made, in Brazil for example, between slavery and the slave-trade, the former being legal, the latter not. In that country breeding of slaves was not interfered with, but importation

of slaves was illegal and, of course, it was the latter which was associated with most, if not all, the cruelty—cruelty and bloodshed in capture, cruelty, disease and death in transit.

The following dates are important to us in connection with this traffic. In 1557 John Lok brought five negro slaves from Africa with the intention of selling them in London, but so great was the indignation provoked that he took them back to their native country. Five years later, in 1562, Sir Richard Hawkins sailed with three ships for West Africa ; there he purchased 300 negroes and sold them in the West Indies. The transaction was so profitable that Queen Elizabeth invested money in similar enterprises and Hawkins then bought 500. Between 1680 and 1700 British vessels, mostly belonging to Bristol owners, carried 300,000 slaves. By the middle of the eighteenth century Liverpool surpassed Bristol and her merchants had eighty-seven slave ships sailing regularly between the Guinea Coast, the West Indies and the Southern States. In the ten years 1766–76 Liverpool-owned ships carried 300,000 slaves at a price of £13,000,000 or so. When in 1807 the Abolition Act was passed Liverpool declared that she was ruined, but by trade in ivory, gum and palm-oil she was able to retain the lead in West African commerce.

It has been stated, graphically if perhaps somewhat melodramatically :

Every tusk, every scrap of ivory in possession of an Arab trader has been steeped and dyed in blood. Every pound weight has cost the life of a man, woman or child ; for every five pounds a hut has been burned ; for every two tusks a whole village has been destroyed ; every twenty tusks have been obtained at the price of a district with all its people, villages and plantations.

We have touched upon the ills and disasters associated with the raiding of villages and capture of slaves, but it was on the journey from the interior to the coast that their real martyrdom began. Underfeeding, overworking, exhaustion from these combined with disease and cruelty resulted in heavy losses to the traders. Much of the hardship inflicted was due to the natural attempts at escape. Lovett Cameron noted at Kilumba the harsh treatment accorded to the unfortunate captives and had no hesitation in asserting that " the worst of the Arabs are in this respect angels of light in comparison with the Portuguese and those who travel with them . . . Had it not come under my notice I should have scarcely believed that any men could be so wantonly and brutally cruel." He observed at one time a gang of fifty-two women tied together in three lots ; some had children in their

arms, others were far advanced in pregnancy, and all were laden. They were covered with weals and scars. To obtain these fifty-two women, at least ten villages had been destroyed, each with a population of one to two hundred, or about 1500 in all. Some of the men, he goes on to say, may have escaped to neighbouring villages, but the majority had been either burned when the villages were surprised or shot while defending their wives and families, or were doomed to death in the jungle from starvation or the attack of wild animals.

To prevent escape the slaves were often kept in chains on arrival at a place for bivouac, only to be released when the caravan was about to start and they were given loads to carry. Men, women and even children

footsore and overburdened were urged unremittingly . . . and even when they reached their camp it was no haven of rest for the poor creatures. They were compelled to fetch water, cook, build huts and collect firewood. . . . The loss of labour entailed by working gangs of slaves locked together is monstrous ; if one pot of water is wanted twenty people are obliged to fetch it from the stream. On the road too, if one of the gang requires to halt the whole must follow and when one falls five or six are dragged down. . . . The poor wretches were travel-worn and half-starved, with large sores caused by their loads and the blows and cuts they had received. The ropes that confined them were eating into their flesh. . . . That so many escaped was a relief to me ; although there was reason to fear that numbers of them died of starvation in their endeavours to reach home, or fell into the hands of others.

Along the caravan routes graves and numerous skeletons, slave-clogs and forks still attached to bleached bones or lying among them testified that many lives had been sacrificed on the march. Even as late as 1859, in a letter to Admiral Sir F. Grey, we find the following :

In chained gangs the unfortunate slaves are driven by the lash from the interior to the barracoons on the beach ; there the sea-air, insufficient diet and dread of their approaching fate, produce the most fatal diseases ; dysentery and fever release them from their sufferings. . . . On a short march, of six hundred slaves intended for the *Emma Lincoln* one hundred and twenty-five expired on the road. The mortality on these rapid marches is seldom less than twenty per cent.

Mungo Park related how the captured slaves, in fear and trembling in the belief that the white men purchase them to eat or to sell them to others for the same purpose, often make desperate efforts at escape ; they are, therefore, kept in irons and closely

watched, or fettered by the leg in pairs, the fetters being held up with a string for walking. Every four are fastened by the neck with a strong rope and for the night their hands also are fettered and sometimes a light iron chain encircles their necks.

In *Discoveries in Africa* (by Denham, Clapperton and Oudney, published in 1828) occurs the following :

The depth of the well at Meshroo is from 16–20 feet : the water good and free from saline impregnations : the ground around is strewed with human skeletons, the slaves who have arrived, exhausted with thirst and fatigue. The horrid consequences of the slave-trade were strongly brought to our mind ; and although its horrors are not equal to those of the European trade, still they are sufficient to call up every sympathy, and rouse up every spark of humanity. They are dragged over deserts ; water often fails, and provisions scarcely provided for the long and dreary journey.

Often the caravan would set out with perhaps only a quarter of the amount of provision required and only the most robust might reach their journey's end and those in a very debilitated state where they would be kept and fattened up again for the market. On one occasion during a day's journey of twenty-six miles Denham counted 107 of these skeletons by the way and on another, only five days later, he writes : " During the last two days we passed on an average sixty to ninety skeletons each day ; but the number that lay about the wells were countless."

We have mentioned already the custom of selling the carriers of ivory together with their burdens on arrival at the coast.

At Gorée, on one occasion mentioned by Mungo Park, the surgeon of the slave ship died and Park himself looked after the slaves. He remarked that at this stage he did not observe any wanton acts of cruelty either on the part of the master or the seamen. The crews, however, were short-handed and the mode of confining and securing the negroes was rigid and caused no little suffering and sickness among them. Three died on the Gambia and six or eight while they remained at Gorée, eleven perished at sea and many of the survivors were emaciated and weak. He remarks on the habit of clay and earth eating, adding " whether it arises from a vitiated appetite or from a settled intention to destroy themselves, I cannot affirm." It was more probably due to, as well as the cause of, helminthiasis, especially ankylostomiasis.

On arrival at the coast the slaves passed into other and usually more humane hands, for the owners were generally good business

men and care of their human merchandize meant higher prices on reaching their destination. The captains of the slave ships had orders, once the purchase was completed, to take good care of the ' cargo ' to prevent any unnecessary loss. The food was to be good, they were not to be maltreated by the crew or those engaged to look after them ; nevertheless, the hardships of the ' middle passage,' as the outward voyage from Africa to the New World was called, were necessarily great. Original cost, maintenance and transport would amount on an average to some £20, whereas on arrival in good condition a slave would fetch four to five times this sum. A long voyage meant greater cost of maintenance, more sickness and mortality and consequent reduction of profit, hence good food and prevention of disease were matters of importance for the trader.

The ' middle passage ' might take as long as six months and the rate of insurance was a premium of 3 per cent. against natural, wilful or violent death, but the insurance companies had a reservation clause relieving them from payment if the mortality was less than 15 per cent. The dangers of overcrowding were well known but were often and, when slave-trading became illegal, were always disregarded. Thus, a vessel 80 feet long and 26 feet wide, with a slave-room beneath the deck of 5½ feet high, and two tiers of boards for sleeping accommodation might have 300 slaves. At another time a ship of only 200 tons might have as many as 600 negroes. A ship of the above dimensions and of about 500 tons burden was the average. There was a hold for provisions, rum, powder and so forth, an upper deck and a 'tween-decks for the slaves who were stowed in this space in hundreds, the men forward, shackled at the start of the voyage, the women and children aft, unchained. They were often thrust in until they were in actual contact and might stay thus, if the weather was bad, for days or even weeks. Some would die and the living and dead would lie chained together in the dark, and hunger and thirst, disease, particularly dysentery from the filth, and misery might on a bad voyage kill off three-quarters of the total. Stories have been told where the packing was so close that some would have to sit between the legs of others, and the boarding above them so low that even sitting upright was not possible ; on arrival ' every conceivable distortion' might be observed as a result of the long cramped position. In smaller vessels the slaves might be kept in these holds for the entire voyage. The stench from such ships was later of value as a diagnostic indication. The bruising of the ill-clothed, even naked and manacled bodies when the ship pitched and rolled

was an additional torment. The quicker-sailing vessels, as the American clippers engaged in the Cuban trade, had only one slave deck in place of three in some of the slower. The actual slave deck was at the foot of a deep hold ; above this, running round the sides, were two platforms ; each adult was allotted a space 5 feet 6 inches in length and 16 inches in width ; the height between the platforms was usually 24, occasionally 26 inches. In one slaver stopped and examined in 1829 there were found 562 slaves so closely stowed that they could not lie down nor change their posture, and this was a ' good ship ' with 3 feet between the decks. If they could be obtained in sufficient numbers the best age for slaves was said to be between eight and twelve years, the reasons being, chiefly that they took up less space and were more easily packed, being stowed sideways on boards. If weather permitted and when they were sufficiently cowed they might be brought up on deck for exercise and for washing, and to allow their quarters to be in some degree ventilated. We have spoken above of a ' good ' ship. There were what was known as ' good ' and ' bad ' ships. In both the overcrowding, the dirt, the low physical condition and general depression would foster disease, but on ' good ' ships the slaves were brought up on deck for a daily bath (in those days such a luxury was not indulged in even in England) and were allowed to stay from 8 or 9 a.m. till 4 p.m. and the sleeping quarters were cleaned ; they were given two good meals, perhaps three, and the sick were removed to special quarters and received special attendance and treatment. On ' bad ' ships conditions must have been truly appalling ; the slaves wedged in, as stated above, they were not allowed on deck, the air was indescribably foul. In rough weather the scuttles would be closed, leaving only gratings which were quite inadequate for ventilation. One captain wrote that he had " seen the slaves drawing their breath with all the laborious and anxious efforts for life which are observed in expiring animals subjected by experiment to foul air or in the exhausted receiver of an air-pump." Thirst was always agonizing and the water allowance on one ship recorded as a teacupful every third day ; we cannot wonder that on such a ship suicides were far from rare.

On short journeys, except that the agony was of less duration, the conditions might be even worse. Lord Palmerston in 1845, quoting Buxton on the East African slave-trade, said :

The dhows were large unwieldy boats without a deck. Temporary platforms were erected, leaving a narrow passage in the centre. The negroes were then stowed in bulk, the first tier being laid along the floor

of the vessel, two adults side by side, with a boy or girl resting between and upon them until the tier is completed. Over these the first platform is laid, separated by an inch or two from their bodies, when the second tier is stowed in the same manner and so on, until they reach the gunwale of the vessel. They calculate that the voyage will not exceed twenty-four hours, or at the farthest forty-eight.

It often happens that a calm, or unexpected land-breeze delays their progress ; in this case a few hours are sufficient to decide the fate of the cargo ; those of the lower portion of the cargo that die cannot be removed. They remain until the upper part are dead and thrown over, and, from a cargo of 200 to 400 stowed in this way, it has been known that not a dozen, at the expiration of ten days, have reached Zanzibar (C. M. Macinnes. *Slave Trade*).

Food and water were difficulties, particularly if the voyage was long. We find in one place that the allowance for 400 slaves conveyed from Guinea to Curaçao was 1800 lb. pork, 800 lb. bread, 320 sacks of groats, 160 sacks of beans, 300 lb. of tamarinds, 5 half-measures of corn spirit, 2 half-measures of French brandy, 3 hogsheads of vinegar, one barrel of tobacco and twelve gross tobacco pipes. We shall have more to say shortly on the diseases of the voyage ; here we may mention that scurvy was a real and constant menace and fresh fruit, fresh meat and fish were obtained whenever the opportunity presented itself. We hear of a slaveship in 1668 filling up with 900 oranges, 5000 lemons, coconuts and pineapples, 90 fowls and two goats, at a total cost of 16 florins.

Water stored from the Guinea Coast was believed to cause diarrhœa, dysentery and guinea-worm, and boiling it was advised, but this was not possible for so large a number. Failing boiling, vinegar or some drops of oil of vitriol might be added.

The death-rate among the slaves, it will be readily understood, varied within wide limits. On a short and prosperous voyage with good weather and opportunities for the captives to come up daily on deck deaths might be remarkably few ; on a long voyage with bad weather, food shortage, an outbreak of dysentery, and so forth, they would be very many. On a voyage from Madagascar to Sumatra, lasting a little more than five months 139 died out of 236 (59 per cent.) ; on another with a cargo of 425 slaves for Surinam only six died. The average mortality was 11–12 per cent., though, as we have just seen, it might be four or five times as great, or, as recorded in 1769 to 1777, only 4 per cent. With humane captains like John Newton in 1754 and Crow in 1806 voyages might be made without a single negro being lost. As might be expected the mortality was often high from communicable infection among seamen engaged in the trade.

There was a general rule that the sick should be separated from the healthy—a rule more honoured in the breach than in the observance. The fate of those taken sick on board was often appalling. Many were thrown over the side, for by the terms of insurance if death occurred on board the loss fell on the owners, if jettisoned as part of the cargo they came under the head of " sacrifice of cargo " and the insurance was paid. The fate of the healthy in the days after abolition when the trade was being carried on surreptitiously was often as bad or even worse ; for if a slaver was being chased and was losing the race the slaves might be thrown overboard *en masse*, eighty, ninety-seven, and even 500 in one instance have been recorded ; sometimes they were placed in barrels in order to delay the pursuing cruiser which would stop to pick them up, at other times they were thrown over still manacled or fettered so that they might not be rescued to give evidence against their captors. There is no doubt that the attempts at abolition made the lot of the slaves still harder during the ' middle passage,' because the vessels engaged in the traffic were fewer, and the number carried at a time was greater to increase the profits and reduce the risks and the insanitary conditions were worse.

Though it has nothing to do with the slave trade, it is interesting to note that the lot of the transported convict in the seventeenth century was no better than that of the slave in the ' middle passage.' On 17th October, 1685, was published *A Memorandum of the Wonderful Providence of God to a poor unworthy creature during the time of the Duke of Monmouth's Rebellion*, by John Coad, one of the sufferers. He states that :

The master of the ship shut ninety-nine of us under deck in a very small room, where we could not lay ourselves down without lying one upon another. The hatchway being guarded with a continual watch with blunderbusses and hangers, we were not suffered to go above deck for air or easement.

They were nearly starved and " our water also was exceeding corrupt and stinking, and also very scarce to be had . . . a great affliction after they came into the hot weather." Without light and fresh air, with almost total absence of ventilation, the hold soon became a fetid human stye where filth fermented.

By which means the ship was soon infected with grievous and contagious diseases, as the smallpox, fever, calenture, and the plague,

with frightful botches. Of each of these diseases several died . . . others were devoured with lice till they were almost at death's dore.

Little imagination is needed for us to visualize the condition of these poor wretches by the time the voyage was over and their destination reached. The state of their quarters may be gathered from the fact that the ships were of so little value that they were often abandoned because nobody could be got to clean them. At some ports there were strict rules regarding disembarking the sick. At Surinam, for example, a surgeon would go on board and disembarkation was permitted only if his report to the Governor was favourable. If there was infection on board the vessel was kept outside until it had subsided and danger of introduction of infection was at an end.

The captives were in most cases mere skin and bone, many half blind, and they had to be carried ashore and three months might elapse before they had recovered sufficiently to be worth being put up for sale. This is confirmed in the account of the *Travels of Lady Emmeline Stuart Wortley and her daughter, Victoria, between the years 1849 and 1855*, who saw a captured slaver at Kingston, Jamaica, soon after it arrived in port. The importer, for two reasons, one because of the weak and emaciated state of the slaves, the other because of the danger of hidden disease, had a 'sanatorium' at his disposal where the wasted, dazed and staggering wretches emerging from the fetid holds of the ship were sent to recuperate.

When the time came for the sale all sorts of tricks were carried out to enhance the value of the human merchandize. By removal of grey hairs, by gay apparel, older men and women might be passed off as young—similar means are adopted in civilized countries to-day and for a similar purpose—and careful toilet was made to cover defects. The sick and disabled would be rejected on the advice of a surgeon who would examine them for physical defects, and for indications of disease, notably hernia, prolapse, venereal disease, cataract, yaws, guinea-worm, elephantiasis, chronic malaria. As we have seen in the chapter dealing with trypanosomiasis, cases of sleeping sickness in an early stage might evade detection. Those who passed the surgeon were then branded with the mark of the purchaser. The latter, however, was usually very cautious, because the initial cost of a slave was heavy. After some such notice as the following (quoted in Macinnes's *Slave Trade*) would-be purchasers would collect, as at an auction, which in fact it was.

Jamaica General Advertiser. January 28th, 1783

" Martha Brae " January 27th, 1783

For Sale

On Wednesday the 4th

of February

On Board the Ship

THARP

Captain Fisher

(From Annamaboe)

Four hundred Choice, Young Fantee, Ashantee and Akim

Negroes

By Thorp and Campbell.

They were then led round like ponies at a horse-fair ; they were made to show their teeth, to run, lift weights ; legs, arms, movements, general build and physique were examined. After being purchased and branded some might be well treated but with others little attention was paid to health conditions. Sickness and mortality were too readily ascribed to the climate. Hospitals were in many places like prisons, built on swampy ground, unprotected from the heat, no bed but the floor, no separation of sexes or of special disease. In health they might be put to work for twelve hours a day, their food for the week a stem of bananas, 1½-2 lb. of salt meat and two or three tots of rum. Natural water was often brackish. In their ' free time ' and on Sundays they could cultivate their own little patches of cassava, potatoes, etc., or rear fowls and ducks, and add to their dietary by catching fish or crabs. When admitted to hospital their diet remained unchanged and the drugs comprised quinine, calomel and opium, but little else. To guard against malingering, and even when sick, if not too seriously ill, they might (as in Haiti) be chained to their so-called beds " lest their illness be too much of a holiday for them."

We can feel no surprise that suicide was on some estates fairly frequent, for many of them had a happy belief that after death their spirits would return to their native lands.

Passing to the medical conditions in a stricter sense the diseases from which the slaves suffered and infections which they were the means of introducing in the countries to which they were imported. Some effort was made to exclude those obviously diseased being taken on board from the barracoons at the port of

embarkation, but among those who would pass the examining surgeon would be some with trypanosomiasis in an early stage, chronic dysentery patients and carriers, those with guinea-worm, hookworm, leprosy, and so forth. With the total absence of sanitation on board and poor food, outbreaks of dysentery would arise and at times cause great loss of life. Ulcers were exceedingly common, the result of infection of small wounds, or of pressure of fetters and manacles in the long journey to the coast. Few people without tropical experience know what an African ulcer may look like; it often spreads both in extent and in depth to lay bare even blood-vessels and tendons and bone and may encircle the limb.

Dysentery was widespread in Africa; the travellers, explorers and pioneers of last century all bear testimony to its attacks. Dysentery and fever among the personnel and escort played a large part in bringing failure to Mungo Park's second African journey. In his last letter, to Lord Camden, he wrote:

Your Lordship will recollect that I always spoke of the rainy season with horror, as being extremely fatal to Europeans; and our journey from the Gambia to the Niger will furnish a melancholy proof of it.

We had no contact whatever with the natives, nor was any one of us killed by wild animals or any other accidents; and yet I am sorry to say that of forty-four Europeans who left the Gambia in perfect health five only are at present alive—viz., three soldiers (one deranged in his mind), Lieutenant Maclyn and myself.

Another of the soldiers died a few days afterwards. Lovett Cameron in the account of his travels frequently mentions his being *hors de combat* owing to attacks of dysentery.

We have mentioned the fact, widely believed in slave-trade days, that the water taken on board from the Guinea Coast was the cause of diarrhœa and dysentery during the voyage. What was called 'white dysentery' was common in slave-ships and among the slaves in the West Indies hepatitis and liver abscess were frequently seen. It is possible, perhaps likely, that the amœbic form was slave-imported, but dysentery, more probably bacillary, was known to exist in America early. Epidemics—and the bacillary is the usual epidemic form rather than the amœbic —were reported in Mexico early in the Conquest and a very severe outbreak ran through the army of Nuñez de Guzman in Nueva Galicia in 1529. Winterbottom writes that in five ships carrying 600–700 slaves each there died of dysentery 250, 220, 150, 60 and 82, bringing the disease with them on board or contracting it from one another on the voyage.

Common diseases among the slaves on board were fever, dysentery and ophthalmia. The last was somewhat mysterious and since it not infrequently resulted in blindness was looked upon with dread by the crew. There is on record the instance of a French slaver, the *Rodeur*, engaged in transport of slaves between the coast of Africa and the French West Indies in 1819 where all except one seaman became more or less blind, and this man reported on arrival at Guadeloupe that he had seen and hailed a large Spanish slave-ship drifting in charge of a sightless crew. Chisholm quotes in his *Diseases of Tropical Climates* a memorandum respecting the French slave-trade, and the *Rodeur* in particular, in which it is said that the crews and slaves enjoyed good health until they reached the equator when *blepharoblenorrhœa contagiosa* broke out among the negroes and spread rapidly till all on board became infected. No reason is given for the delay in onset.

The sufferings of the people and the number of the blind [he writes] augmented every day, so that the crew was seized with the dread of not being able to make the West Indies, only one of them having escaped the contagion, on whom their whole hope rested. Thirty-nine of the negroes had become perfectly blind, twelve had lost one eye and fourteen were afflicted with blemishes more or less considerable.

Of the crew, originally twenty-two, twelve lost their sight entirely, among whom was the surgeon, five lost one eye and four were partially injured.

As for malaria there can be no doubt that many of the slaves were infected and since no small proportion was, in some cargoes, children there were sure to be carriers of the infection. Enough has been said elsewhere as regards scurvy on ship-board; among the slaves, whose diet was even more restricted than that of the crew, and who relied for fresh air and exercise on being allowed up in fine weather to " dance round the deck to the sound of the drum," scorbutic conditions were common and severe—swollen, bleeding gums, loss of teeth, hæmorrhages into the muscles, were often observed. Trotter in 1792 reported on one ship several fatal cases till, on reaching Antigua, a supply of fresh vegetables was obtained and given to the slaves during an eight-day passage from Antigua to Jamaica which did much to restore their health and " repair them for market so that they were sold later at what was called a very high price."

In America, North, Central and South, in the various colonies to which the slaves were imported, the diseases they brought with them must have been a serious menace and in fact in time became

public health problems of the highest importance ; in the words of Sir Harry Johnston, the negro was " a hive of dangerous germs." It can be affirmed almost with certainty that the slaves introduced leprosy, filariasis, dracontiasis, uncinariasis (ankylostomiasis), yaws and yellow fever. The last less certainly than the others (this has been discussed in the chapters on Yellow Fever). Alastrim is another disease probably introduced, for inoculation against smallpox was carried out in Africa from very remote times.

After arrival in their new homes they fell ready victims to diseases already present there, notably tuberculosis and, next to that, syphilis. Tuberculosis finds a ready soil in the tissues of the native—the susceptibility of the black races to the infection has been common knowledge for many years, and when, as servants they come to live in closer contact with their masters and mistresses and the children of these the menace to the white man is great.

To make the tale complete it will be of interest to add a few words contrasting the condition of the slave before and after abolition, though this is of medical import indirectly only.

The capture, the journey to the coast, the ' middle passage ' to their destination were accompanied by much diabolical cruelty and hardship, but once established at work their lot was often far from unpleasant. They were too valuable a property to be wantonly damaged. In the earlier days of slavery they had a fair proportion of leisure time—one day a week for cultivating their own plots of ground, on Sundays and on some church festivals work was forbidden (in Spanish colonies), the total came to 134 days a year at their own disposal. They had facilities for marriage, magistrates were appointed to safeguard their interests and they were allowed, in fact were entitled, to purchase their freedom at an adjudicated price and proprietors would take a pride in furthering the well-being of their slaves.

Happy the slaves that were in such a case ! They were certainly no worse off than the children working in the mills of Lancashire and Yorkshire. On some plantations the master would pay an apothecary to visit the slaves daily and a house was set apart as a sanatorium where those who were sick received proper treatment. Contrast this with the conditions given in a letter by a man named Oastler in the *Leeds Mercury* of 1830, where we read of children working nineteen hours a day, with fifteen minutes off for breakfast and thirty minutes for dinner, and for a full week the pay was 3s. 7½d. Even Wilberforce, the ruling purpose of whose life was emancipation of the West Indian negro, did not

seem to appreciate the horrible plight of these poor children in the mills of the north.

There were other proprietors, however, who would repudiate or violate all legal claims and in pursuit of their own gain would ruthlessly overwork their slaves. This was much more marked after abolition of the trade. Whereas previously, in Cuba for example, the average annual output of sugar per man was one hogshead, it became as much as three tons. There was no Sunday off in the season of crop, any who dawdled, and some would even fall asleep at work exhausted, would be stimulated by the lash, and the working life of a negro instead of thirty years or more was reduced to ten or at most twelve years.

The termination of the war between North and South in America was also practically the end of systematic free medical service for the poor—the regular medical and sanitary care of the negro slaves. After 1864 the extension of disease among the emancipated gave cause for alarm and the health of the whites after the exhaustion and privations of the war was far from good. Along with other aspects of Southern culture medical service, hygiene and health administration also suffered. We see in the medical arrangements of some present-day commercial and industrial concerns the analogue of the free medical service for slaves and a strict sanitary regimen on the plantations.

Portuguese slaves in Brazil were on the whole treated quite as humanely as the Spanish mentioned above, though some estate owners were cruel and unrelenting in exacting work. A British planter in Jamaica with an estate bringing in about £800 a year acknowledged that if he had worked it in the unprincipled way of some of his neighbours he could have made it yield nearly twenty times as much.

The British Sugar Act of 1846, by which British ports were opened to receive sugar from Brazil, gave a vast impetus to the slave-trade and numbers imported were more than doubled, from 19,000 to 50,000 in the year. Many deaths resulted from an outbreak of yellow fever, 16,000 are said to have perished in Rio de Janeiro alone. In 1850 the number of slaves imported was 23,000, after which there was a rapid diminution owing to suppression of sailing slave-ships by faster travelling steamers. In 1851 there were 3000, in 1852 only 700 imported.

For some time before abolition there was a general feeling that slavery was not right and many owners, when dying, would grant freedom to their slaves—there would not seem to be much credit to the proprietors in such a death-bed repentance. Nevertheless,

such a feeling was kept in check until, at the end of the eighteenth century, came the judicial decision that slavery could not exist in England and any slave succeeding in escaping to England was automatically emancipated.

Attempts at abolition made the lot of the unfortunate captives all the harder during the transport, because the risk of capture and loss of cargo led to many more being carried at a time, worse overcrowding and most appalling conditions of insanitation, to make one voyage yield the profit of two previously, and if he was chased the captain might show little hesitation in lightening the ship by jettisoning some of his human cargo in order to allow him to travel more speedily and to retard his pursuer who would stop to pick up some of the unfortunates (see also p. 994).

Denmark was the first to forbid her subjects, in 1792, to engage in the slave-trade, by a Royal Order of 16th May, ordering its cessation in all Danish possessions at the end of 1802. America followed Denmark two years later, prohibiting exportation of slaves. Ten years afterwards an Act prohibiting further introduction of them was revived. In 1807 Great Britain abolished the trade so far as her subjects were concerned, and in 1814 France came to a 'left and right' decision; on the one hand agreeing that the trade should be stopped and on the other signing a treaty that while the trade continued with French colonies it should be carried on by French subjects only. The following year a decree was passed putting a stop to the trade altogether in five years, but not till 1848 was slavery in the French colonies abolished, though the traffic was continued under the guise of 'indentured labourers' from the East Coast of Africa. By their terms of service they were to be repatriated at the end, but this was often postponed on some excuse or other or even refused altogether, and it was not till 1896 that slavery was really abolished in the French colonies.

Similarly in West Africa; the employment of slaves had brought great prosperity to São Thome, Príncipe, Dahomé and Angola. Abolition ruined Príncipe altogether and São Thomé temporarily, the latter recovering when quinine and cocoa cultivation were taken up. The Brazilians in 1860–80 developed industry in Angola by steam navigation of the Kwanza and by a railway linking up São Paulo de Loanda with the interior. From 1880 under the guise of 'apprenticeship' slavery began to revive. The negroes were landed in São Thomé, having been sold and bought; if paid at all their payments were very irregular, and they rarely

if ever regained their liberty. They were on the whole kindly treated. H. W. Nevinson in his autobiography describes the procedure. Legally, these negroes are ' contracted labourers,' and legally the children of such are free. The labourer works for nine hours daily on days " not sanctified by religion," with an interval of two hours for rest. He is under bond for five years, not to leave " except in order to complain to the authorities," while the employer on his part binds himself to pay a monthly wage and to provide food and clothing. As regards this and slavery there was mere distinction without difference. Each native before engagement was asked formally whether he (or she) was willing to go to work in São Thomé (or Príncipe). Usually no answer was given, or if it was no attention was paid as to whether it was affirmative or negative, for those asked had been brought on account of having violated native customs, or broken some Portuguese law, or been charged with witchcraft by the local medicine-man when a relative had died ; others presented themselves to acquire the wherewithal to discharge an ancestral debt, or were sold by maternal uncles ' to whom all children belong ' ; some served as indemnity for village wars ; some had been raided on the Congo frontier—here we are approaching very close to the old slave-trade methods—others were changing masters because when too old for work on the mainland it was not an uncommon practice for them to be shipped to São Thomé. The annual average was 4000 to 6000 for São Thomé and Príncipe. On landing at the former they were taken to the Curador's office and assigned to various planters ; then assembled in gangs and marched off to the plantation. After a rest of two or three days they were set to clearing bush or gathering and sorting the pods. When the five-year term was up the planter would collect them in batches of fifty or so, send for the Curador and parade them before him. In the presence of two witnesses and his secretary the Curador would inform them that their contract was renewed for a second term of five years and they were dismissed to their labours again.

In 1820 Great Britain paid to Spain £400,000 for a promise that she would cease to purchase negroes in Africa—a promise often violated by individuals. For twenty years after nominal abolition one after another of the Captains-General of Cuba supplemented his emoluments by a tribute or hush-money from the dealers of a doubloon a head on each negro imported with his consent and even connivance. The practice was stopped by an order under which every slave had to be registered by the planters,

and the magistrates were empowered to order a slave muster and any not legally enrolled were liberated.

Portugal decreed restrictions in the trade in 1815, agreeing to abolish it north of the line on condition she was not molested in the south. This arrangement was nothing less than farcical and it was not until 1874 that slavery was abolished in Cape Verde Islands and in the other Portuguese colonies the succeeding year.

In 1833 slavery was abolished in Jamaica and the West Indies. The author some twenty-eight years ago conversed with one who had been a slave shortly before abolition and he spoke of it with regret, saying that they were better looked after and cared for in the old slavery days than after emancipation when they had to look after themselves. Britain paid £21,000,000 to the owners in the West Indies and Cape Colony (where slavery was abolished in 1833–40) by way of compensation. Her penitence was further shown in the generous contributions to founding Sierra Leone as a slave-settlement, in helping Liberia which the American Colonization Society had established for the repatriation of slaves in 1820, and in patrolling the eastern and western coasts of Africa and the Persian Gulf to intercept slavers. In short, Great Britain concluded twenty-six treaties with the civilized powers and sixty-five with native chiefs relative to the slave-trade. C. M. Macinnes gives a much higher figure and says that in the seventy-five years subsequent to British abolition the Government signed some 600 treaties and international instruments designed to check or abolish it, eighty of them with Portugal alone.

In short, slavery was abolished by the French in all their possessions in 1848, by the Dutch fifteen years later, in 1863, by the Portuguese in African possessions in another fifteen years, 1878 ; in Cuba and Porto Rico, held by the Spaniards, in 1886, and for two years more Brazil was a slave-holding country, in fact the traffic ceased only when the markets were closed to the trader. The Sultan of Zanzibar in 1873 after considerable pressure ruled that in his Sultanate the trade was illegal, but nevertheless it continued to flourish until the British and Germans took over the administration—in short, so long as any part of the African coast was under Mohammedan control there was slave-trading and slave-raiding in the hinterland ; in fact, until the French occupied Wadai and the Italians Tripoli and Cyrenaica.

There is no question that emancipation was right ; there is no doubt also that too great results were expected to accrue and that quickly. The negro from time immemorial was a servile race ; after emancipation he was free to work or to idle and with soil so

fertile he could almost live without working. It is undeniable that the slaves were sometimes and in some places—not in all by any means—ill-treated, but in many cases no labourer in any country was so cared for and so protected ; he was saved from the wants and anxieties incident to labouring classes ; he was clothed, fed, given quarters and, if needed, hospital treatment. The negro's idea of emancipation was freedom, not from slavery, but from work—he was content to lie in the sun and eat breadfruit and yams (preferably those belonging to someone else). Jamaica, for example, before emancipation was a land of wealth ; afterwards, within ten to fifteen years, half the sugar estates and more than half the coffee plantations had fallen back to bush, because labour became scarce and wages high, so that a negro could live for a week on a day's wages ; land was forced out of cultivation and the morale of the natives deteriorated. Jamaica in fact did not recover until a new generation of negroes grew up for whom consistent and regular work became a necessity and they no longer regarded the hiring of their service as a degradation, but saw that the conditions were equitable and there was dignity in labour. Santa Martha had been a fruitful sugar-growing country ; after emancipation in 1851 labour was not procurable and bush grew up and the only part of the earth to give her increase was the provision grounds of half-caste Indian squatters.

The negro, unless he worked on compulsion, was the most indolent of human beings. In slave times, as has been said before, he was generally happy, well fed, looked after medically, and not as a rule harshly treated, though his hours were long, but his lot, it has been written, was " better than that of many a labourer in . . . some parts of England," and " better than that of the free cultivator of the plains of Lombardy."

Better than sudden emancipation would have been to interpose a period of paid service by which the negro would acquire voluntarily the habit and discover the benefits of working. As it was he was an irrational, improvident child without thought for the morrow, and many on discharge were reduced to starvation or thieving. Emancipation made him free as no English labourer is free. The latter cannot select whether he will work or not, he works under ' free ' conditions of work. He is not free to be idle if he is to live.

In spite of all that is done to educate the negro many have doubts whether he can be educated out of his primal instincts— this applies to the generality ; there are notable exceptions, of course.

The belief that the African is capable of living as hygienically and morally as the Caucasian was the great mistake made by those who deal in abstract principles. Thus come about insanity and tuberculosis, and perhaps syphilis. Education, as understood by the white man, will never in the full-blooded African affect centres above those governing the procreative instincts. . . . With the advent of puberty all intellectual development ceases.

This certainly seems to have been borne out by American experience. In Charleston, Augusta and other places where the problem has been studied, there is a strongly prevalent opinion that nearly every negro who has reached middle life has suffered or is suffering from venereal disease or its results. In 1912, writes Shufeldt (*The Negro. America's Greatest Problem*),

there are about ten million negroes in the United States, 87,000 in Philadelphia alone. Hospital experience enters at some time into the life of nearly every city negro, and hospital records show that practically all male city negroes indulge in promiscuous illicit intercourse and carry with them venereal disease. It is the exception in hospital experience for a male negro to fail to admit having been infected with both syphilis and gonorrhœa. . . . Treatment is rarely carried to the point of cure.

In the United States emancipation led to more active hybridization. Concubinage in the Southern States is destroying the integrity of the negro races, raising up a menace to the white man, lowering the standards of both races and preparing the way for riot, mob, criminal assaults, and finally a death struggle for racial supremacy. " Teach the negro girl art, music, and literature, she will become a concubine at the first opportunity " (Attorney J. H. Currie).

What happens when the emancipated slave is repatriated and left uncontrolled or under his own control we shall see later.

The abolition of slavery led to the Indentured Coolie system, the overpopulated East being called upon to provide workers for the West Indian plantations. The Anti-Slavery Society tried hard to prevent this immigration of coolies. They did not succeed ; in 1852–60 ten to twenty thousand of them were brought to Trinidad from Madras and Calcutta, and in the two years 1855–7 its imports increased by one-third and its exports by two-thirds, and the island passed from distress to prosperity.

In spite of all the resolutions and legal enactments suppression of the slave-trade was far from easy. We have stated already how the lot of the slave in transit was made worse because the vessels were more than ever overcrowded to make up for the fewer voyages. Though detection involved a penalty of £100 for every slave carried, together with confiscation of the vessel and its cargo,

it was said that if one venture in three succeeded the profit was good. As in most legal enactments there were wide loopholes for escape. Vessels suspected of trading in slaves could be searched, but, however strong the suspicion, they could be detained only if slaves were actually on board. Hence the practice was to assemble the victims on shore and not to embark them until darkness and a favourable breeze made sailing comparatively safe, and, as we have seen, if pursued and losing the race the masters would avoid technical guilt by throwing the negroes overboard.

Even after capture of the vessel the difficulties were not ended. Law Mathieson relates that the vessel might have to be taken to some more or less distant port for adjudication, and, of all the duties that could fall to the lot of those engaged on this service those of a prize crew must have been among the worst. They had to live, perhaps for weeks, on a foul and possibly pestilential ship with a swarm of half-stifled negroes whose sufferings they could do nothing to alleviate. Mathieson relates the case—which, one would think, must have been most unusual—of an officer named Denman who in 1834 was placed in charge of a slaver, " a rotten ship—a mere wreck upon the waters "—which had been captured when her voyage to Rio was nearly completed. There were 400–500 slaves on board. The Mixed Commission at Rio found that the ship was not Brazilian but Portuguese and Denman had to take her to Sierra Leone, a journey which took him forty-six days. At Sierra Leone the ship was released because, though Portuguese, she had been captured south of the line (see above, p. 1003) and the master was allowed to take her back to her originally planned destination. There must have been no little delay, both at Rio and Sierra Leone, for Denman was four months on board and " witnessed the most dreadful sufferings human beings could endure." When he left the ship before the third voyage 104 of the slaves had died. Here the attempt to put down the trade had aggravated its cruelty, for prior to capture there had been only seven deaths.

Let us end this section on a more cheerful note by contrasting the present state of treatment of negroes in the United States with the past which has been sketched in the foregoing pages. In 1936 (United States Department of the Interior Bulletin) there were 129,000 negro boys in Georgia ; playgrounds and community centres for negroes had been provided. In Washington, D.C., Jacksonville, Florida, Indianapolis and Cincinnati, Ohio, are special golf-courses for coloured citizens. There are also centres for education and recreation with swimming-pools. In Augusta,

Georgia, are health clubs, sewing and cooking classes, music classes, classes for adult education, scout groups, gymnasia, etc. Groups for hiking, camping, for drama, social meetings, dancing and so forth.

There is a vast difference between the educated native and the native *tinged* with education. The latter has no enterprise, application or energy. When he wishes he can use his brain—more often by devious ways to unlawful ends—but in general he loathes physical fatigue, he resents discipline and despises manual labour as a regular occupation. The former, the right native properly educated, presents a marked contrast to this. Some of the Fulani, for example, have shown themselves extraordinarily apt with the theodolite and " will work out complicated problems in mathematics with the assurance of a senior wrangler." Others can be trained to do medical work, not merely routine as nurses and dressers, but as medical practitioners capable of assuming responsibility, as those trained at Suva, Fiji. But this applies to exceptional cases ; in general, as Alan Lethbridge has stated in his interesting work *West Africa the Elusive :*

> It is impossible to hurry a race forward in the course of a few years to a stage which it would not otherwise have reached for several centuries, except by paying the inevitable penalty for interference with any such natural law. The civilization acquired or imposed by such artificial means is for the most part no more than a veneer, which is easily peeled off and has the terrible disadvantage of adding to the vices and defects incidental to the new condition without having first eradicated those that previously existed, while it also tends to destroy those better qualities that were inbred in the subject in his natural state.

We have now arrived at the last stage in the history of the slave-trade, so far as it concerns our subject, namely Repatriation. This was not nearly such a simple matter as might appear. It was no more easy to found a black colony in an inhabited part of Africa than a white one. The existing inhabitants would almost certainly rather find room or make room for white people than for more blacks. Medical questions would also bulk largely, for the repatriated would have lost the resistance or immunity to disease which their forefathers had enjoyed. So when in 1816 the American Colonization Society, seeking the welfare of some 200,000 freed slaves, planned to return them to their native land and found a free colony for them, they made some preliminary investigations and the erstwhile slaves arrived in 1818 on the Grain Coast under the tutelage of American white men. Within

a short time many were attacked by sickness, and large numbers died. Such of the Americans as survived abandoned the enterprise with loss of health. In 1822 there were some new arrivals. A good proportion of each new group was attacked by fever. Thus, of 107 brought by one ship all were down within a month of landing, and of another batch of the same number, twenty-four died. In 1827 more freed negroes from Baltimore, Maryland, and Washington, D.C., memorialized Congress for aid in the emigration and transport of all those desirous of going to Liberia.

Liberia boasted of one of the rainiest and most humid climates of Africa. The unhealthiness of the coast is due to this. The average mean temperature is 76°–80° F., with very little variation from season to season and the relative humidity is very high, *the air often being nearly saturated.*

The repatriated negroes built Monrovia, so named in honour of President Monroe, and formed the settlements which developed into the republics of Liberia and Maryland, the former being recognized as a sovereign and independent State by Great Britain in 1847 and by the United States in 1861. Since 1847 its Government has exercised full sovereignty over a territory of 35,000 square miles, equal in extent to Connecticut, New Jersey, Massachusetts, Maryland and Delaware together. Contradictory reports have been given as to the result. According to some " the inhabitants have developed further than those left in the United States and have shown that the negro can organize and maintain a civilized government." According to others they had by 1920 relapsed into a state but little removed from that of the primitive negro. No census had been taken ; property owners had a vote in the general management, and these were estimated at about 6000, nevertheless at a Presidential election 51,000 votes were cast of which the President elect received 45,000, and in 1927 the majority in votes was 125,000. From the general health point of view, sanitation did not exist—there was no health organization ; the streets had no pavements, but at the side were gutters in which at certain seasons Anopheles and Aëdes bred abundantly ; there was no proper water-supply ; drinking water came from rain collected in cisterns or wells in the porous soil of the backyards in which was also dug the latrine unprotected from flies ; there was no system of sewage disposal. Food for sale is not protected from flies, houses are not screened, nor are mosquito-nets in general use.

On the outskirts of Monrovia was a large cemetery with an undrained, insanitary swamp where clothes were washed and in

which Anopheles and Culex breed, separating it from the residential quarter. The inhabitants are lazy and take little trouble to cultivate the soil. Gilbertian as it seems there are, however, ice-plant, electric lighting and a telephone system. The old Americo-Liberian families are dying out, partly from disease (see later), partly from a low birth-rate, and partly from polygamy with the aborigines, though they do nothing for the latter and adopt an air of superiority to them.

It is quite true to say that in its early sense slavery does not exist, but the Americo-Liberian will in exchange for a small present to the chief take the children of the aborigines for house-work or other. Wives, children and women in general are of small account except as goods and chattels, and may be pawned. Among some it is hardly possible to distinguish the status of a wife from that of a purchased slave ; the man buys his wife and she becomes his property ; he clears a piece of land in the forest and sets her to cultivate it. All the produce belongs to the husband, when the wife has planted and cultivated it and gathered in the crop.

R. P. Strong's Harvard African Expedition to Liberia and the Belgian Congo (from which the above information has been gleaned) in 1926–7 did much to benefit the natives by establishing clinics in the towns and villages which he visited. Strange to say, they found the villages and houses fairly clean, although chickens and goats have equal right of entry into the huts with their human owners and often sleep in them. The houses are—and they must need it—swept clean each day.

Of diseases present there is a goodly variety. According to Strong's report the following are prevalent : *Malaria* which is more common on the coast than in the interior. Of thirty-six Kru children examined thirty-one had parasites in their blood ; in the interior about 33 per cent. of the inhabitants examined had parasites and 16 per cent. had spleens more or less enlarged. *Filariasis* caused by *W. bancrofti*, with elephantiasis, is common, as also are infections by *Loa loa*, *F. perstans* and *Onchocerca*. *Schistosomiasis* of the rectal type, *S. mansoni*, is common. Other infections by no means rare are *leprosy, yaws* and *syphilis*. Yaws is very prevalent, but syphilis is said to be absent in north-west Liberia. The condition known as *n'gonde* is tertiary yaws. *Juxta-articular nodules* are frequent, but whether due to trauma, to yaws, or to syphilis is not certain. *Gangosa* and *goundou* are both fre-quently seen. Ulcerating and granulomatous conditions of the skin are common, and *ainhum* is very prevalent in the interior, and in several cases the fourth as well as the little toe is affected.

Smallpox and *chickenpox* occur, also *tuberculosis*, and venereal diseases, especially *gonorrhœa*.

A few cases of *yellow fever* were seen and there is no justification, says Strong, for supposing it to be imported whenever cases occur. Between February and June they saw eleven cases, six of them fatal and two of the patients were American citizens. *Trypanosomiasis* was not seen by members of the expedition though it has been noted by Johnston and by Maughan as having been present early in the nineteenth century. It is certainly not common now.

In spite of what should have been favourable circumstances and environment the outcome of repatriation has not been very successful. With the outbreak of the American Civil War immigration almost ceased, the original founders and pioneers of the new Republic died out, the older members of those who were left and the younger generation had no energy or initiative, preferring to rely on America or Great Britain for getting anything done, conditions fell from bad to worse until, in 1912, America, on appeal, took over control of Liberian finances and a general supervision of her affairs—a plain and unequivocal answer to the question " Will the negro use his freedom with a man's sense of responsibility ? " If he will not work voluntarily, cultivate his land and set his house in order, then poverty, unreliability and circumstances in general will in the ordinary course of nature relegate him again to a position little better than that of his forebears.

In seeking and in striving to educate the negro—in this as much as in any condition of life—we must not be in a hurry. ' *Festina lente* ' leads most quickly to the end desired ; it is useless to attempt to force European customs and manners upon a people at present unfitted for them. The forcing system has been tried in various colonies, but it merely puts on a veneer of spurious civilizatɩon and the subject of it acquires and adds to his native stock of vices those of the people he is learning to ape. We must not expect too much and to hope to see the results of our efforts in our own lifetime *is* to expect too much.

CHAPTER XXIII

SOME BRIEF BIOGRAPHIES

In this section we propose to present brief sketches of the lives of a few of the more important or better known of those who devoted their chief interests to tropical medicine. No attempt will be made to write their biographies, that is, to go into detail; our aim is merely to set before readers those incidents of their lives which had a bearing on tropical conditions and medical research.

Wonder will very likely be expressed at the omission of certain names which others feel merit notice. The reason for their exclusion here is that those who have studied but one problem, or have made but a single contribution to tropical medicine, have already received notice in the section dealing with the particular disease they described, such as Laveran and malaria, Koch and cholera, Loos and ankylostomiasis, Hansen and Danielssen in leprosy, and any further details, however interesting as general biography, would be outside the scope of this work. Others again, such as Sir John Pringle, Sir Gilbert Blane, Sir Pardey Lukis, Timothy Lewis, E. A. Parkes, Desgenettes, were engaged in general tropical medicine and its practice or in tropical hygiene and did not undertake any special work of a pioneer character ; they too have been mentioned in the body of this work.
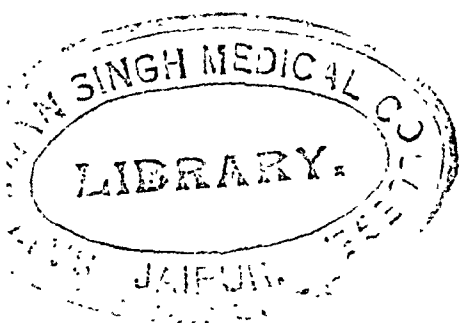
JACOBUS BONTIUS

(1592–1631)

For the past three centuries the name of Jacobus Bontius has had an honourable place in Holland and no student of the history of tropical medicine should be ignorant of his claims to renown. Though his medical life was short it was crammed with experience which he embodied in a book, the first Dutch work on tropical medicine. He was born at Leyden in 1592 where his father, Geeraerdt Bondt, was Professor of Medicine and of the " liberal arts and sciences connected therewith " at the University. Geeraerdt de Bondt had received this appointment in 1575 and he held it till his death in 1599. In addition to his duties in this post he had been elected in 1587 teacher of botany in succession to Rembertus Dodonæus. He had three daughters of whom little has been recorded and four sons, three of whom at least attained renown. The eldest, Reinier, who graduated in medicine just before his father's death, was, a month after that event, appointed Assistant Professor of Philosophy at Leyden University. In 1606 he was ' extraordinarius ' and the following year ' ordinarius ' of medicine and was also physician-in-ordinary to Prince Maurice. Jan, the second son, was also a doctor of medicine and later held the less professional position of municipal tax-collector at Rotterdam. The third son, Willem, was Professor of Law at Leyden from 1615 to 1618 and in the succeeding year was sheriff of the town. Jacobus, the fourth son and the best known of the family, dedicated his *De medicina Indorum* to this brother whom he always looked upon as his confidant, guide and mentor.

In May 1604, in his twelfth year, Jacobus was registered as a *studiosus artium liberalium* and ten years later, on 22nd June, 1614, graduated as Doctor of Medicine. He practised for a time in Leyden and saw the outbreak of plague there in 1624–5. His success, financially at least, was not great in his native town and in a letter to his brother Willem he states that he intends to try his fortune in the East Indies, where he " hoped his talents would be more appreciated." He was a man of wide reading, for he speaks of his library of about 2000 choice volumes and expresses
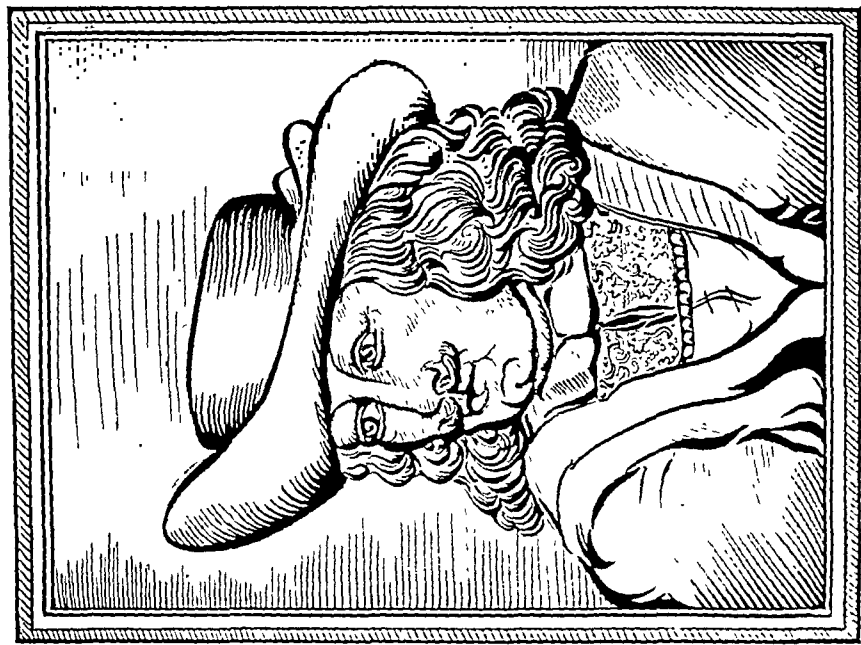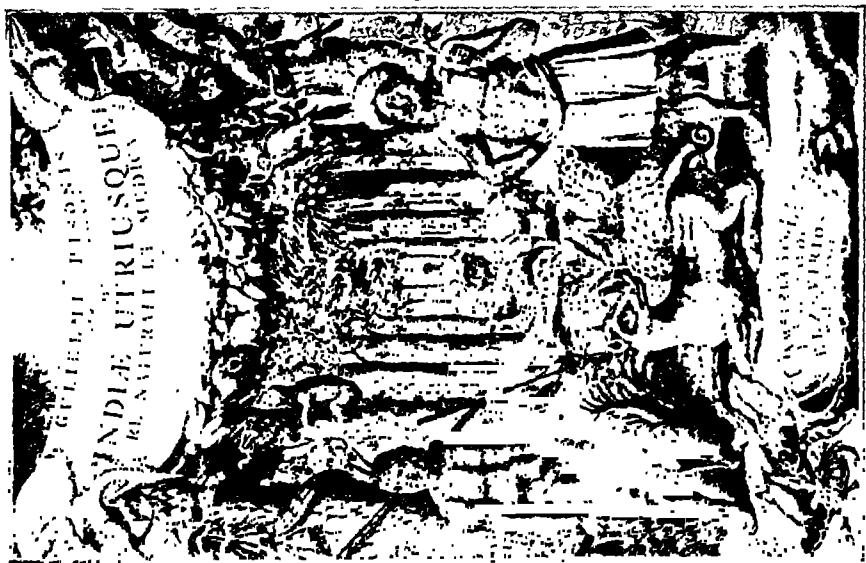
TITLE PAGE OF PISO'S WORK PUBLISHED IN 1658.

JACOBUS BONTIUS.
1592—1631.

the hope that on his return he may obtain a professorship of medicine.

Botany was in those days an important part of medical training and not an independent branch of science, and all those setting out for the East Indies, new colonies in which scientific men at Leyden took great interest, were asked to send or bring home bulbs and roots for planting in the Botanical Gardens and for the purpose of study in the University.

Bontius' botanical leanings were fostered both by the need of knowledge of the science in his profession and also by the teaching of his father, though he was but a boy of seven when his father died. On his applying for service in the East, the East India Company was only too glad to employ a medical man who had knowledge of plants and would be able to collect specimens and reliable data on them in the Indies. In 1602 there was issued a " Memoire voor die Appoteckers ende chirurgins, die in het jaer 1602 op de vloote naar Oost-Indiën vaeren sullen " (Memorandum for the Apothecaries and surgeons sailing on the fleet to the East Indies in 1602) and in this many Indian herbs were mentioned.

Jacobus Bontius received his appointment as ' doctor, apothecary and surgical inspector ' from the Directors of the East India Company on 24th August, 1626, and he sailed with his wife, Agneta Jansz, and two sons, Jan and Cornelis, the latter only two years old, on 19th March, 1627. On the voyage about a score of the crew reported sick and were thought to be suffering from scurvy, but " after being spoken to in vigorous language " they got up and returned to work. The voyage was broken by a stay at the Cape where Bontius noted the beneficial effects of fresh food on those afflicted with scurvy, particularly, he says, *Trifolium acetosum*, a herb growing there in abundance. This is now known as *Rumex acetosa*, or sorrel, which contains acid potassium oxalate and tartaric acid and was for long used in the treatment of scurvy. The only risk was of oxalic acid poisoning if the plant was taken in excess.

Bontius' wife died on the voyage, but we are not told the cause of her death. On the 13th September, nearly six months after setting sail from Holland, he arrived at Batavia, but almost at once proceeded to the Moluccas. He describes the blindness (see below) from which many of the crews of vessels sailing to Timor suffered. The following year (1628) he returned to Batavia and experienced the hardships and rigours of the siege by the Javanese from August that year to the beginning of 1629. During this time of stress the sickness and mortality rose enormously.

So many women and children, as well as men, have died [he writes] the people have been obliged to live so cooped up that many foul smells and diseases resulted. All the canals round the ramparts of the town have become cesspools and filled up, by which reason many perish in poverty, misery, disease and dirt.

He ascribes the dysentery to pollution of the river by the dead bodies which the Javanese threw into it. He certainly studied the connection between the circumstances of the people and their general health and in his first book he discusses the personal hygiene of the European in the tropics, in the section *De conservanda valetudine.* Swaving goes further and attributes the health measures adopted in Batavia after 1628 to the influence and efforts of Bontius.

He and all his family—he had married again, the name of his second wife being Sara Gerardi or Geraadt—suffered from dysentery and soon after recovering from this he himself was attacked by beriberi. The Governor of the Colony, Jan Peitersz. Coen, a patron and staunch supporter of Bontius, died of dysentery in September 1629 ; Bontius attended him in his last illness.

In June that year Bontius had been appointed member of the Court of Justice and in 1630 was chosen by the new Governor for the office of Attorney-General and later for a short period he " officiated as a bailiff." These many public duties interfered considerably with his scientific studies. His *Methodus medendi* and *Observationes* were ready for the press in 1629 and the quality of these is certainly of a higher standard than the *Diæta sanorum* and *Annotationes* of two years later.

Bontius' second wife died in June 1630 of cholera and soon afterwards he lost his elder son, Jan, from smallpox. Early in 1631 he married again, his third wife being Maria Adams, widow of the Predikant Joannes Cavalier, who had died of dysentery in 1630. Jacobus Bontius himself died on 30th November, 1631, in his fortieth year ; the cause of his death is not known. All we read is that " sickly in body lying in bed, but in perfect possession of his wit, memory, senses and power of utterance " (sieckel, naer den lichaem, te bed liggende, doch syn volcomen verstandt, memory, sinnen en intspraecke wel hebende end gebruyckende als Kennel was ende bleeck), he passed away ; he had lived for four years in a bad climate in times of stress and had suffered from more than one serious illness.

We must speak of his work in a little more detail. He certainly did not spare himself. Only two years after arriving in Batavia

he had written ' in the night hours ' his *Methodus medendi* and *Observationes*, based on his experiences in hospital and private practice. We see, on reading them, that he seized every opportunity of acquiring knowledge of disease and information on the use of herbs from local sources. He found many herbs of benefit in the diseases prevailing there ; acid and astringent plants effective in cholera and dysentery, and he speaks highly of the herbal knowledge of the native women to whose hands, he says, he would rather trust himself than to some " learned medical man or conceited surgeon, proud of their scholastic knowledge and swollen with prejudice, who without any experience and burdened with book learning have, God save the mark (God beter 't) the audacity to call themselves thorough doctors."

His aim in the *Methodus* and *Observationes* seems to have been to write a practical manual and he gives a résumé of the chief symptoms of a disease, discusses the probable cause and the indications for treatment, stating what had proved most efficacious in his own hands, and not infrequently he is able to round off his account by a description of the post-mortem findings. These are undoubtedly the most important of his works, and his descriptions, though brief, in many cases are so clear that we can recognize even to-day diseases such as beriberi, cholera, dysentery and yaws. As regards the first of these he deals only with the dry, atrophic form ; of the wet, œdematous form he speaks under the heading of hydropsy. Reading his remarks on cholera one is led to believe that he did not distinguish between true cholera and other severe diarrhœas—few, if any, did as early as Bontius' day. In March 1631 he writes to his brother, Willem, that his [second] wife Sara died of " een vehemente cholera, die heer so regneert als die pest ten onzent " [vehement cholera raging here as the plague does with us], and he quotes the case of a man (among many) who suffered from violent diarrhœa and vomiting with pains and convulsions [he may have meant cramps] and died in six hours. If this had been a unique case we would think of acute food poisoning, but as one of several it is in favour of true cholera. His personal experience of dysentery, in himself, members of his family and among his friends, enables him to describe it in accurate detail ; he believes in its infectivity, though he remarks that the outbreak in which he was himself a sufferer was due to dead bodies of men and animals remaining unburied or thrown into the river, polluting the air and water. He gives an account of abscess of the liver and its surgical treatment, but there is nothing to indicate that he recognized any connection between this and dysentery. His

description of ' Amboyna smallpox ' fits very closely what we now know as yaws or frambœsia, and he points out the differences he had noted between it and venereal disease (syphilis).

In his earliest days in the East he had noticed that impairment of vision, even to actual blindness, was wont to attack sailors going to the Moluccas and he had the perspicacity to ascribe this to some nutritional disturbance—the natives, with whom he seems to have been inclined to agree, believed it to be due to eating warm rice—and he recommended shark's liver eaten raw with salt, and the local application of shark's liver oil to the eyes.

In the work *Historia plantarum (de plantis et aromatibus)* Bontius describes not merely the plants themselves but their medicinal properties, their ' aert, krachten en werckinge,' *i.e.* their nature, power and effect (or action). He tested many of the native medicaments and in the *Historia plantarum* many new plants find a place in treatment. At the same time he is not forgetful of the overlapping of empiricism and magic in folklore and native medicine. Prior to going East he studied the writings of Garcia da Orta, Monardes, Clusius and others and his *Animadversiones* are comments on some of the publications of the first named of these.

His *De conservanda valetudine* is written in Latin in the form of dialogue. Bontius answers leading questions put to him by a hospital surgeon, Andreas Duraeus. It is interesting reading; Duraeus does not disdain to appear as an ignoramus and thus extol the wisdom of his preceptor.

Bontius' industry must have been astounding. To have achieved so much in the short space of four years, when he was at the same time engaged in hospital and private practice and in official duties, and, moreover, was often far from well, is a matter indeed for wonder.

Piso's work entitled *De Indiæ utriusque re naturali et medica,* in fourteen books, published at Amsterdam in 1658 contains much of Bontius' investigations to which is added a commentary by Piso. The latter also published some of Bontius' notes, reference to which Bontius made in a letter to his brother, Willem. Bontius, however, died before he was able to complete or even amplify the notes. Piso's work mentions the six books of Bontius and continues :

In quorum librorum penultimo, Naturæ Animalium, Avium et Piscium, ultimo autem Arborum et Plantarum species miræ, Europæis incognitæ, ac ad vivum delineatæ, explicantur.

Commentarii

quos Auctor, morte in Indiis præventus, indigestos reliquit

a

Gulielmo Pisone

in ordinem redacti et illustrati, atque annotationibus reru*n et iconum necessariis adaucti.

How these Notes of Bontius came into Piso's hands is not known. It is conjectured that Bontius' widow sent them to the Governors of the East India Company and that they passed them on to Willem Piso whose work is concerned with the East and the West Indies.

Piso acknowledges in his own work that he has incorporated the writings of Bontius " to prevent their being published in a mutilated form." Piso's book *is a large folio published by the* brothers L. and D. Elzevir, and combines Bontius' work with his own *Historia naturalis Brasiliæ,* which had been issued separately ten years before.

In 1769 was published an English version of the first four books of Bontius, evidence of the value of the author's pioneer work. This was reprinted at Amsterdam in 1931. The name of Jacobus Bontius deserves to be held in honour and veneration as the first to regard tropical medicine as an independent branch of medical science.

DAVID BRUCE
(1855–1931)

David Bruce was born in Melbourne, Victoria, on the 29th May, 1855. Five years later his parents left Australia and came to Great Britain, settling in Stirling, where their son, David, attended the High School. He left school when still young and from fourteen to seventeen years of age was in the service of a commercial firm in Manchester. Till then he had been a lad of unusually robust health and this, fortunately, enabled him to overcome a severe attack of pneumonia which, however, left its mark and seemed to render him susceptible to pulmonary attacks later in life. At the age of twenty-one he entered Edinburgh University with a view to studying zoology, a subject which had interested him from childhood and which imparted a trend to his subsequent outlook on medical problems. Thus, although he deviated to medicine his earlier studies probably influenced him in his regard to disease, in that he would approach a problem from the biological standpoint, and the laboratory and experimental side would make a greater appeal to him than would the clinical. The accuracy of his deductions from observations in the field has found abundant confirmation in the rarity with which they have subsequently been proved erroneous.

In 1881 he graduated in medicine and came south as assistant to Dr. Stone, a practitioner in Reigate. The latter's predecessor was Dr. J. S. Steele whose daughter, Mary Elizabeth Steele, born in 1849, was married to Bruce in 1883. She was, for the remainder of their joint lives, chief assistant to her husband; she inherited her father's artistic attainments and by her skill not only did she illustrate his researches, but she worked with him at home and abroad, taking part in his investigations in field and laboratory, sharing in all the discomforts and hardships of the former, while, as regards the latter, much of the technical work of the laboratory in connection with the investigations was performed by her. She had acquired knowledge of laboratory technique in Koch's laboratory in Berlin where the Bruces worked in 1888. Bruce himself never lost an opportunity of expressing his indebtedness

PLATE V.

SIR DAVID BRUCE.
1855— 1931.

[Photograph kindly lent by Sir Arthur English.]

to his wife for her skilled aid and on his death-bed—they died within a couple of days of each other—he particularly asked that her part in his scientific work and attainments should receive due acknowledgment in any record of what had been accomplished.

Private practice did not prove very congenial and he entered the Army Medical Service. He was commissioned Surgeon-Captain on 4th August, 1883, and the following year was ordered to Malta. There he found that a large percentage of the military and naval personnel and of the civilian population suffered from prolonged fever whose origin was obscure, and which was known as Malta Fever. Later, when its distribution was found to extend along the Mediterranean littoral, it was called Mediterranean Fever, and later still, when its geographical range was proved to be far wider, Undulant Fever, from the character of the temperature chart (see Undulant Fever).

Bruce was aware of recent bacteriological discoveries—of the organism of typhoid fever by Eberth in 1880, of that of tuberculosis by Koch in 1882, and of the diphtheria bacillus by Klebs in 1883—and attacked the local fever problem from the same angle. Within two years he discovered a ' micrococcus ' in the spleen of persons dead of the disease and proved by experiment its ætiological significance. At first called *Micrococcus melitensis* it was later, in 1920, placed by Tensier and Meyer in a separate genus, *Brucella*, in honour of the discoverer. The results of following up Bruce's discovery, the consequent eradication of the disease from the Army and Navy at Malta on the findings of the Malta Fever Commission in 1904–06, of which Bruce was Chairman, have been described in the chapter dealing with this disease and need not be repeated here. Although this research was carried out by a young Army Medical Officer in the course of his routine duties, his findings have remained unchallenged.

His first leave, in 1888, was spent by his wife and himself in acquiring further technical skill and learning up-to-date methods in Koch's laboratory and on their return to England in 1889 Bruce was appointed Assistant Professor of Pathology in the Army Medical School at Netley, a post which he held for five years. He then was sent to South Africa, in 1894, and was stationed at Maritzburg. Sir Walter Hely-Hutchinson was at the time Governor of Natal, having previously been Lieut.-Governor of Malta in 1885–6 when Bruce was occupied in elucidating the cause of the local fever. The Governor, becoming acquainted with the fact that domestic animals in Natal were suffering severely from a condition known as nagana. and having had experience

of Bruce's acumen and scientific ability, asked that the latter might be seconded to investigate it. In a report published in December 1895 Bruce was able to state that he had discovered in the blood of the affected animals a trypanosome which later came to be known as *Trypanosoma brucei* (see Trypanosomiasis).

Aided constantly by his wife, Bruce from field and laboratory researches showed that this trypanosome was actually the cause of the disease and that it was conveyed by the bite of the tsetse fly. Thus, the fly-disease on the one hand and nagana on the other were shown to be, not two different diseases, but one and the same. Again practically all his conclusions have stood the test of time and subsequent study.

In 1895 he received promotion to the rank of Major; he saw active service in the War in South Africa and was present at the battles of Elandslaagte and Laing's Nek. He was with the besieged in Ladysmith and diverted his abilities to operative surgery. In 1899 he was elected a Fellow of the Royal Society *in absentiá*. For his work in Ladysmith he was promoted Lieutenant-Colonel in 1900, and his wife, as ever his efficient helpmeet, acted as theatre sister and also took part in nursing the sick; she was awarded the Royal Red Cross.

Bruce's next work was, as one of a committee, to investigate enteric fever and dysentery in the army in South Africa, their prevalence, causes and prevention. In 1901 he returned to England and the following year presented the Committee's report to Parliament. In 1902 also the Royal Society was requested by the Foreign Office and the Colonial Office to investigate the Sleeping Sickness of Uganda and accordingly the Society sent out a Commission. In 1903 the War Office, at the request of the Royal Society, seconded Bruce to join the Commission and he was sent out to take charge of the work. How he confirmed Castellani's finding of a trypanosome in the cerebrospinal fluid and, following it up, found it also in the blood of these patients at an earlier stage of the disease, and how he demonstrated the co-existence of sleeping sickness with the distribution of the tsetse fly have already been related (see Trypanosomiasis).

In August the same year he returned to England, having added another stone to his scientific monument and proved that sleeping sickness in Uganda was a form of trypanosomiasis conveyed by a tsetse fly, *Glossina palpalis*. In December 1903 he was promoted Brevet-Colonel and in the following year was awarded a Royal Medal of the Royal Society. In 1904 also he again visited Malta as head of the Royal Society's Malta Fever Commission,

which demonstrated the part played by goats' milk in spreading infection. In 1905 he was created Companion of the Order of the Bath and three years later a Knight Bachelor. In 1908 he was again in Uganda and followed up the work of Kleine regarding the cyclical, as opposed to the purely mechanical, transmission of the trypanosome by Glossina.

In 1911 he was pursuing the subject of sleeping sickness in Nyasaland and working on the *rhodesiense* species of trypanosome and its conveyance by *G. morsitans*. The next year he received special promotion to the rank of Surgeon-General. As Commandant of the Royal Army Medical College for five years, 1914–19, he was unfortunately debarred from service in the field during the European War, but was employed in research as Director of the Trench Fever Committee and in prevention of tetanus in the field. In 1918 he was created Knight Commander of the Order of the Bath, and from 1917–19 was President of the (later Royal) Society of Tropical Medicine and Hygiene. Other offices worthy of mention held by him were that of Chairmanship of the Lister Institute, membership of the Army Medical Advisory Board, of the Tropical Disease Committee of the Royal Society, and, in 1924, the Presidency of the British Association.

Besides the honours already mentioned he was awarded the Buchanan Medal of the Royal Society in 1922 ; he was a corresponding member of the Academy of Sciences, Paris, and Foreign Member of the Paris Académie de Médecine. Further, he was the recipient of several honorary degrees, conferred by the Universities of Liverpool, Glasgow, Dublin, and Toronto.

Sir John Rose Bradford, who knew him well, stated that Bruce was

a man of fine presence and physique and possessed in youth [before his attack of pneumonia] great physical strength. He was rather reserved and distant in manner . . . and very downright and outspoken in speech, which was apt to be caustic on occasion. The most marked features of his character were his straightforwardness and his extreme contempt for all sham and want of complete honesty. . . . He was absolutely loyal to his friends and junior fellow-workers and, when his reserve was penetrated, a very charming companion.

JAMES CARROLL
(1854-1907)

James Carroll was born in Woolwich, England, on 5th June, 1854. At the age of fifteen he emigrated to Canada and in 1874 entered the United States Army and while still in the Army began to study medicine at the University of the City of New York, starting on this career considerably later in life than is usual, namely at the age of 32 years, in 1886. He continued for a year and then, after another year's interval, resumed his medical studies in 1889 at the University of Maryland, Baltimore, and graduated in 1891.

The next two years he spent at Johns Hopkins University doing post-graduate work in pathology and bacteriology. In 1893 he entered the Army Medical School at Washington where he met Walter Reed.

During the ensuing seven years he seems to have been engaged in the routine duties of his profession, but in 1900 he was selected for special duty as a member of the United States Yellow Fever Commission to Cuba, as second in command under Reed, and acted as chief when in August Reed returned to the United States. During the two months of Reed's absence Carroll passed through an attack of yellow fever acquired experimentally by a mosquito bite. There is on record a note made by his nurse : " Says he got his illness through the bite of a mosquito—delirious."

His recovery from this illness was thought to be complete, but when convalescing he had a ' heart attack,' a " feeling of acute distension and fear of arrest in diastole," indicating myocardial mischief and he clearly had some sequela, for he was rejected by an insurance company because of his heart, either a valvular lesion or relative incompetence due to myocardial change.

Reed returned to Cuba in November. While giving all due credit to Reed for his planning of the experimental work we must remember that the carrying out of the experiments largely devolved on Carroll. Reed himself fully acknowledged this ; so much so that the Commission's reports were signed by both.

On 4th March, 1901, Carroll left for the United States but

returned to Cuba in August to continue some experimental work in inoculation of blood and of serum. As has been related (see Yellow Fever) Guiteras had been obliged to stop his work in this direction because two of his subjects died. Carroll, however, adhered to his plan and the published report of these experiments was the last communication issued under the joint authorship of Reed and Carroll. It was entitled : *The Etiology of Yellow Fever. A Supplemental Note*, and was read at the Third Annual Meeting of the Society of American Bacteriologists, Chicago, 31st December, 1901, and 1st January, 1902.

In 1903 Carroll published two more papers on the *History, Cause and Mode of Transmission of Yellow Fever*, and on *The Transmission of Yellow Fever*. In the latter he notes that

The greatest obstacle to the control of the disease is the failure to recognize the first cases, when they are not accompanied by black vomit. Some of these cases are so mild that no physician would dare to pronounce them yellow fever unless he knew the disease to be prevailing at the time.

In the next two years, 1904–06, Carroll published five papers all dealing with some aspect of yellow fever, the last on 17th March, with the title : *Without Mosquitoes there can be No Yellow Fever.*

His death, the result of myocarditis, itself a complication of the attack of yellow fever in 1900, occurred on 16th September, 1907.

OSWALDO CRUZ
(1872–1917)

Oswaldo Gonçales Cruz was born on 5th August, 1872, at São Luiz de Parahitinga, in the State of São Paulo, Brazil. His father, Dr. Bento Gonçales Cruz, was Director-General of Hygiene. The year of the birth of their son, Oswaldo, the parents moved to Rio de Janeiro. In 1892, at the age of twenty years, Oswaldo Cruz obtained his medical degree at Rio, the subject of his inaugural thesis being the *Conveyance of Bacteria by Water*. He then entered the National Institute of Hygiene, which had been founded by Professor Rocha Faria, to study bacteriology. Four years later he crossed to Paris and studied toxicology at the Pasteur Institute.

Attracted by the work of the American Commission in reforming the sanitation of Havana, Santiago and other places, and also in the matter of transmission of yellow fever by the mosquito, in which he firmly believed, he made up his mind to apply the like principles to Rio de Janeiro where yellow fever was rife. In the period 1891–4 there were 14,445 deaths from it and in 1896 another 2929. Accordingly he returned to Brazil and was fortunate in obtaining a sympathetic hearing from the President, Rodrigues Ales, and support for his views on rendering Rio sanitary and in particular for establishing port sanitation and in combating yellow fever.

Having obtained the necessary authority Cruz inaugurated his system which involved as far as possible extermination of mosquitoes by attacking their breeding sites and preventing contact between adult mosquitoes and infected patients. In March 1903 he was appointed Director-General of the Office of Public Health, having on his staff seventy-five physicians and a large force of labourers, together with some under instruction. On 20th April isolation of patients was established. Members of his 'brigade' were disposed over the city cleaning out all detected breeding sites, or facultative sites, of Aëdes ; from 8th March notification of cases was made compulsory, together with many other diseases, notably plague, cholera, smallpox, diphtheria, typhoid, typhus, leprosy, malaria, puerperal fever and pulmonary tuberculosis.

The result of these measures is evidenced by the following figures : Whereas in 1903 there were 584 deaths from yellow fever and 360 from plague, in 1908 there were no fatal cases of the former and only 54 of the latter ; by 1912 there were none of either plague or yellow fever.

By many his work in cleaning up Rio de Janeiro is regarded as of secondary importance only since he but followed the example of the Americans in Havana, but it should be remembered that the population of Rio was greater, considerably greater, than that of Havana, Santiago, Panama and Colon together. Cruz subsequently extended his work by applying the measures he advocated to the whole of Brazil.

In 1908 he resigned the Directorship of Hygiene to become head of the Institute for Tropical Diseases, now the Oswaldo Cruz Institute at Manguinhos, Rio de Janeiro. This was a Government institution originally established as the *Instituto Sero-therapia Federal* in 1901 for the preparation of antiplague serum. Later, other antisera were prepared there so that Brazil was rendered totally independent of outside aid.

The original name of the Institute was changed by the Brazilian Government to show honour to the work Cruz had accomplished. He remained Director till his death on 11th February, 1917, in his forty-fifth year.

From this Institute has issued many important reports of scientific work carried out there and published in the *Memorias*. These were the work of many young doctors who went to the Institute for study and research ; of these Oswaldo Cruz selected the best and most promising to become his assistants, or rather colleagues, undertaking special investigations. Carlos Chagas, who discovered and recorded the condition of American trypanosomiasis, called after him Chagas's Disease, was one of these and the protozoon was named *Schizotrypanum* (now *Trypanosoma*) *cruzi* in honour of his master. Oswaldo Cruz was, as his eulogist Dr. Arthur Neiva says, " one of those very rare phenomena among Brazilians—a man of action."

Few men, indeed, can have accomplished what he did in seventeen years of public life. He remodelled the public health of Brazil in three years and the *Memorias* bear witness to the mass of work which emanated from him and the Institute which he directed. He and his assistants were accustomed to work for fourteen hours a day and Prowazek, after several months there, ventured to remonstrate and suggest an annual holiday of a month —a matter which had never, it would seem, presented itself to the

mind of Oswaldo Cruz. Cruz was made an Officer of the Legion of Honour by the French, and one German University nominated him for its honorary doctorate, but his death in 1917 took place before the latter could be conferred.

PLATE VI.

JOHN EVERETT DUTTON.
1877—1905.

JOHN EVERETT DUTTON
(1874–1905)

John Everett Dutton was born at High Bebington, Cheshire, on the 9th September, 1874, and was the fifth son of John Dutton, a chemist. From his fourteenth to eighteenth years he was educated at King's School, Chester, after which he studied medicine at Liverpool. His career there was exceptionally brilliant ; he obtained the Gold Medal for Anatomy and Physiology, and in 1895 the Medal for Materia Medica ; in 1896 the Medal for Pathology. He qualified in 1897 and was awarded the Holt Fellowship in Pathology ; for six months he worked at the Royal Infirmary as Assistant to Professor Rushton Parker and Richard Caton.

.In 1900 he visited Nigeria as a member of an expedition from the Liverpool School of Tropical Medicine, with H. E. Annett and J. H. Elliott, to investigate malaria and filariasis. Their report on the latter was the most complete of any published on the subject. In 1901 Dutton obtained the Walter Myers Fellowship at the Liverpool School of Tropical Medicine and in the autumn of the same year visited the Gambia—this was the School's sixth expedition—and wrote an excellent account of the antimalaria campaign there. In December 1901, an eventful year for him, he recognized in the blood of a patient under Dr. R. M. Forde, Superintendent of the Bathurst Hospital, a trypanosome, a genus of protozoa till then known in animals only. This he described in 1902, calling it *Trypanosoma gambiense*, and the disease with which its presence was associated, but without connecting the parasite with sleeping sickness. The findings of Castellani and Bruce in connection with this disease are fully detailed in the chapters on African Trypanosomiasis.

In September 1902, Dutton was associated with J. L. Todd, in the tenth expedition from the Liverpool School, to study trypanosomiasis in the Gambia and Senegal, and in 1903 they, together with C. Christy, went to the Belgian Congo to observe and investigate the local diseases. Here Dutton turned his attention chiefly to tick-borne relapsing fever. The following year he demonstrated relapsing fever in monkeys conveyed to them by

infected ticks, *Ornithodorus moubata*, a fact discovered in Uganda a few weeks before by Ross and Milne.   Dutton was not able to show the transmission of relapsing fever to monkeys by larval ticks.   Dutton himself contracted the disease and died of it in the Congo on the 27th February, 1905, at the early age of thirty-one years.   The spirochæte of Central African relapsing fever has been named *Spirochæta duttoni* and the Liverpool School of Tropical Medicine founded a Chair in Entomology in his honour, the first Professor being Robert Newstead, F.R.S., who was appointed in 1911.

JUAN CARLOS FINLAY
(1833–1915)

Carlos Finlay, the name by which the great Finlay is generally known, was born in Puerto Principe (now Camagüey), Cuba, on the 3rd December, 1833, the ' cholera year ' in that island. He was christened with the names Juan Carlos, and as he was always accustomed to sign himself Carlos Finlay he transposed his names when in course of time his son, Carlos Eduardo, began the practice of medicine, to distinguish the father Carlos J. from his son Carlos E. Finlay. This brief memoir deals only with the senior, Carlos J. Finlay.

His father was Edward Finlay, a Scottish physician, and his mother was a Frenchwoman, Isabel de Barrés. In his infancy his parents emigrated to Havana and until he was eleven years of age he lived either there or on one of his father's coffee plantations at Guanimar, being educated by his Aunt Anna who had formerly kept a school in Edinburgh, but had left it to live in Cuba with her brother.

In 1844 the young Carlos was sent over to France and he studied at Havre till 1846 when he had an attack of chorea which left him with a stammer. He returned to Cuba where his father succeeded in curing him, but there remained throughout his life a slowness and a slight defect of speech.

In 1848 he returned once more to Europe with a view to proceeding to France to complete his education, but this was a time of revolution, or at least of disorder, there and Carlos stayed for a time in London, followed by a year's residence at a school at Mentz on the Rhine. On leaving this he entered a college at Rouen. While there he passed through an attack of typhoid fever and in 1851 returned to Cuba to convalesce. His studies in France were not considered sufficient for his Arts degree in Cuba and he was consequently debarred from studying medicine there ; he therefore went across to Philadelphia where a degree in Arts was not a necessary preliminary to taking the medical curriculum.

Finlay graduated in medicine from Jefferson Medical College on the 10th March, 1855, when he was a few months over twenty-

one years of age. At the College his special preceptor and mentor was Dr. S. Weir Mitchell, who also proved his life-long friend, then lately returned from working in Claude Bernard's laboratory in Paris. His friend tried to persuade Finlay to settle in New York where Spaniards were many and Cubans not a few, but the latter had other views. In 1856 and the following year he accompanied his father to Lima, Peru, and tried to build up a practice there but without success, and they returned to Cuba. In 1857 he ' incorporated his diploma ' (that is, we understand, was given an *ad eundem* degree) in the University of Havana. Three years later he travelled once more to Paris for special study and in 1864 was in Matanzas, endeavouring to establish a practice, but in 1865 came back again to Cuba and on the 16th October married Adela Shine of Trinidad. He then settled down to practise in Havana, visiting his wife's home in 1869.

In 1865 he wrote his first paper on the ætiology of yellow fever and presented it to the Academy. This dealt with the alkalinity of the atmosphere of Havana which he believed played a part in the ætiology of this disease and he studied the question more minutely during the next four years and did not abandon it till 1880 when he turned his attention to a search for a trans-mitter and began to work on a new theory which he enunciated at the International Sanitary Conference held in Washington in 1881. It was the American Commission of the National Board of Health for the investigation of yellow fever in 1879 that stimulated Finlay to this study and particularly their view as to its infectiousness. He attended the Washington Conference as the representative of the Cuban Government and made there his first public communication on the transmission of yellow fever by a mosquito. Between 1881 and 1900 he published altogether eighty contributions to medical literature, seventy of which were concerned with yellow fever.

At the outbreak of the Spanish-American War Finlay offered his services to the American Government—he was then 65 years of age—and saw active service round Santiago. Returning to Havana he continued unceasingly his efforts to draw the attention of the medical public—Army Medical Officers, Government Medical Officers, and the medical press of the United States—to his views, efforts which at last culminated in the American Mission being sent to Cuba (see also Yellow Fever, and Life of Walter Reed). Finlay met them in the friendliest spirit and offered his whole-hearted co-operation and later expressed his admiration for their methods and modern technique. *He tells how, when he was*

PLATE VII.

JOSIAH CLARK NOTT.
1804—1873.

CARLOS JUAN FINLAY.
1833—1915.

[*Photographs kindly lent by the Lond n
School of Hygiei e and Tropical Medicine*
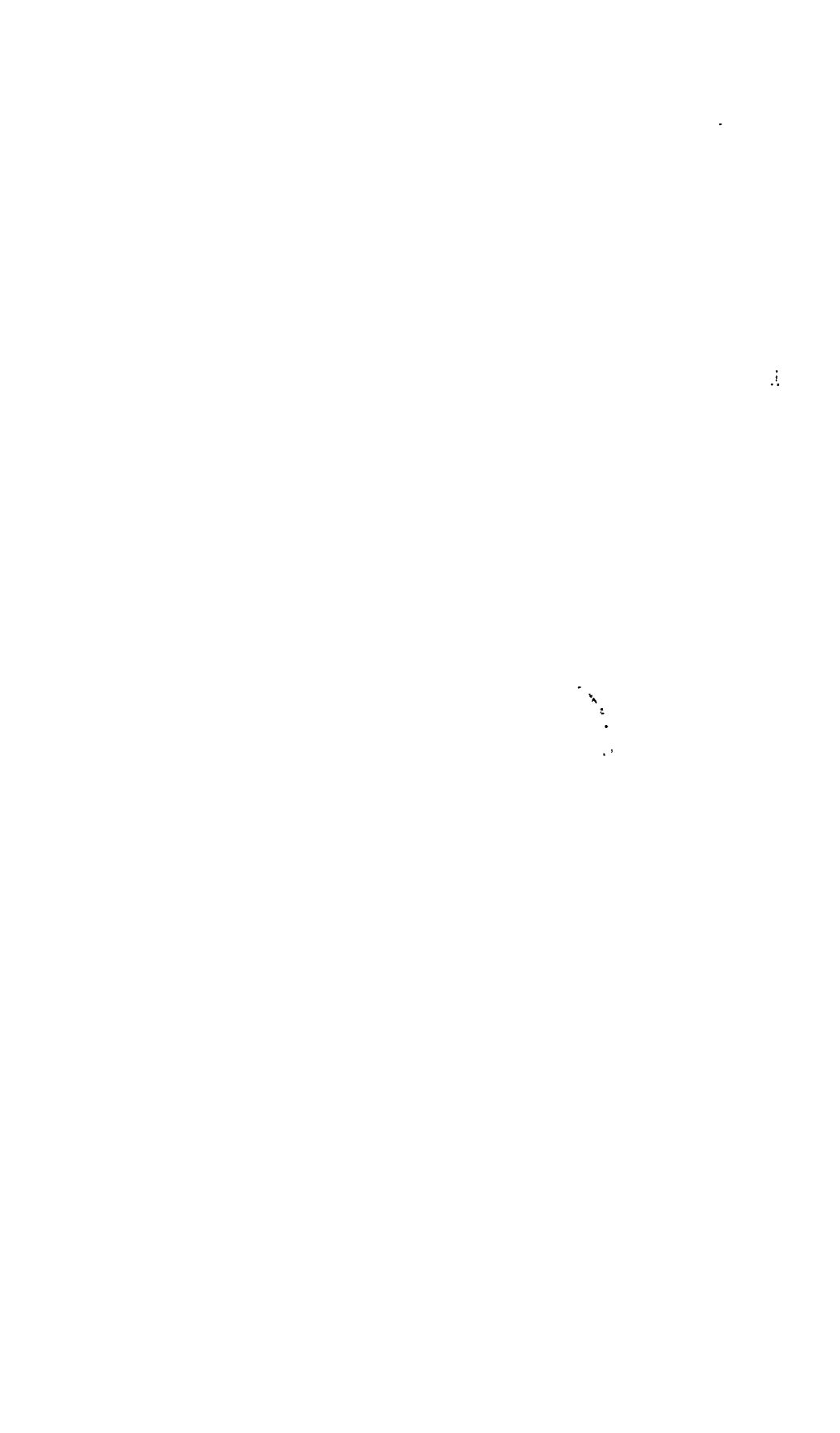
trying to prevail upon Gorgas to put into effect his anti-Culex measures, Gorgas said that at Las Animas Hospital in Havana —which was reserved exclusively for yellow-fever patients and where the nurses were Americans—they had not had a single case of contamination in spite of the presence of mosquitoes. Finlay replied with the definite statement, " At Las Animas there are no ' Culex ' mosquitoes " and though many mosquitoes were caught and killed there were no ' Tiger ' mosquitoes.

It is a matter for wonder to us in these days to think how Finlay had selected this mosquito out of so many species. His argument may be briefly summarized thus : The mosquito lived only below a certain altitude and yellow fever prevailed within the same limits. The temperature most suitable to the mosquito was that at which yellow fever appeared to thrive, and reports showed that mosquitoes always abounded where the disease prevailed. Nevertheless, he had unfortunately never succeeded in demonstrating the truth of his theory (or belief). We must remember that in 1881 little was known of the association of insects with disease. In 1880 Manson had discovered the connection between Culex and filariasis, but this news had not reached Cuba by that time.

In 1902 Finlay was appointed by the Cuban Government Chief Health Officer and President of the Board of Health [Jefe de Sanitad de la República y Presidente de la Junta Superior de Sanitad]. In the course of, or as the outcome of his duties he attended various meetings on health questions in the United States and in October 1903, when he had passed his seventieth year, his genius and geniality were recognized by his being elected President of the American Public Health Association for the meeting to be held in Havana in January 1905.

Finlay's work on yellow fever is apt to put his other accomplishments in the shade. In 1903 he applied himself to the problem of tetanus neonatorum. He got Dr. Davalos to examine the ' wick ' which was in general use for ligaturing the umbilical cord and it was found on many occasions to be infected with tetanus. Finlay then prevailed on the Health Department of Cuba to supply for maternity cases aseptic packets for the proper treatment of the cord. In 1902 infant tetanus was responsible for 1313 deaths, in 1910 this figure was reduced to 576. Between 1865, when his first contribution to medical literature was written on yellow fever, and 1912 when his last was issued on cholera he had 159 to his credit, including 90 on yellow fever, and others on

goitre, cholera, tetanus, ophthalmology (to which he had a leaning since his early days in Paris), leprosy, filariasis, trichiniasis and other helminthic infestations, and beriberi. Mathematics, chess and philology were his hobbies and in them he found relaxation from his medical investigations.

He was an exception to the rule that a prophet has no honour in his own country. He was awarded a pension by the Cuban Government in 1909, and his services are recorded on a marble monument of him in Havana. Outside his native land he received other honours. He had been elected an Honorary Fellow of the College of Physicians of Philadelphia, his alma mater conferred on him an honorary Doctorate of Laws ; in 1907 he was given the Mary Kingsley Medal, an award of the Liverpool School of Tropical Medicine ; in 1908 he was made an Officer of the Legion of Honour of France.

His Scottish parentage is held to account for his intensity and ardour in pursuing the aim he set before him and for his logical theorizing on his subject ; his French parentage explains his amiability, courtesy and imaginative powers, though towards the end of his life the burden of his years seemed to oppress him and made him melancholy and depressed. His death took place on the 20th August, 1915, in his eighty-second year.

GARCIA DA ORTA
(1490(?)———)

Garcia da Orta was the first known European writer on tropical medicine. The exact date of his birth is not known but is said to have been about 1490, at all events "at the close of the fifteenth century." His early years, the time when his intellectual faculties were as "wax to receive but marble to retain," were those when the controversy was strong between the Arabian school on the one side adhering to the tenets of Avicenna and Rhazes, and on the other the 'new school'—new at the beginning of the sixteenth century—urging, even demanding, a return to the teachings of Hippocrates and Galen, medicine having, as it were, gone full-circle and the old again becoming new, Paracelsus standing complacently aloof from both, of whom Jayne writes :

Absorbed in his own dogmatic theories and vowing that his shoe-buckle—the buckles of Philippus Annolus, Paracelsus Theophrastus Bombastus von Hohnheim—contained more medical knowledge than all the treatises of Galen and Avicenna put together.

Another independent thinker was Garcia da Orta, though from all we know of his character and history less aggressive than Paracelsus. He received his degree probably about 1525 ; he was certainly practising in Alemtejo the following year. In 1530 he moved to Lisbon where, being a physician and a botanist, he was appointed Professor of Logic, and where a celebrated mathematician, Pedro Nunes, was Professor of Metaphysics.

Europe at this time was hearing reports and rumours of the marvels of the East and "the fumes of India penetrated the scholastic retreat of Lisbon University." Da Orta became interested, was caught by the glamour and left Portugal for the Orient, travelling by the usual route of the time, *viâ* Cape Verde Islands, Algoa Bay, Mozambique, Mombasa, from there across the Indian Ocean, passing the Lacadive Islands and by Madras to the Malabar Coast. Rarely did the voyage take less than six months, usually more. Da Orta took seven months and,

also usual in those days, the voyagers suffered severely from scurvy.

Camoens, who was a contemporary of Da Orta, wrote concerning Vasco da Gama's first voyage to India :

> A dread disease its rankling horrors shed,
> Ghastly the mouths and gums enormous swelled,
> And instant, putrid like a dead man's wound,
> Poisoned with fetid streams the air around,
> No sage physician's ever watchful zeal,
> No skilful surgeon's gentle hand to heal
> Were found : each dreary mournful hour we gave
> Some brave companion to a foreign grave.
>
> (Mickle's translation.)

Da Orta appears to have been a successful practitioner and one who followed, in a truer spirit than many of his contemporaries, the finer characteristics of his profession in not placing foremost the question of fees. The East fascinated him—the climate, the plants (it will be remembered that he was a botanist also), the productions of the country, the people, their customs and their diseases, and he travelled extensively over India and Ceylon. The scientific study of drugs till this time can hardly be said to have existed at all, empiricism ruled treatment. Da Orta studied them from the botanical aspect, their cultivation and the means by which they might be protected from the ravages of insect pests, and from the aspect of the physician studied the manufacture of drugs from the plants, their standardization and adulteration, not neglecting the cost and the commercial side, and what nowadays is generally included under the term ' pharmacognosy.' All these points were attended to, so far as he was able and had the opportunity in respect of manna, opium, aloes, acacia, black pepper, camphor, stramonium, gamboge, sandal wood, nux vomica (which was unknown before his time), cinnamon, cardamoms and some others. He went further and investigated the rearing of medicinal plants with a view to increasing the content and potency of the drugs obtained from them and he established a botanic garden where Bombay now stands. Professor Frederik August Flückiger, who was born in Switzerland on 15th May, 1828, and has been called the " founder of modern pharmacognosy," referred again and again to Da Orta and stated that no one had described the medicinal plants of India so carefully and so accurately, and his statements have almost invariably been confirmed by later investigators. " The historian of Asiatic drugs must of necessity refer often to Garcia da Orta ; his defects are few and may be

attributed rather to lack of modern instruments of precision than to any other cause."

Cholera, though probably not unknown to medical men in Europe in da Orta's day, had never been described with such wealth of detail prior to the work of da Orta, which may truly be regarded as a classic. India was attacked by epidemics of this disease more than once in the sixteenth century (see Cholera) and in 1543 an outbreak occurred in Goa where da Orta was the vice-regal physician. The Viceroy, a man of advanced views and certainly ahead of his times, ordered post-mortem examinations to be carried out on some of the patients in the hope that something ' might be revealed to assist in treatment or prevention. The physician's description of the findings and of the clinical symptoms is very detailed.

Dysentery was another disease which he saw and described with much detail in both acute and chronic forms and from the accounts there can be little doubt that he met with both the amœbic and the bacillary forms. Under his descriptions of *fevers*, intermittent and continuous, a number of conditions were included and we seem to recognize malaria, typhoid, tuberculosis and possibly kala azar amongst them. He gives an account also of the symptoms in cases of cobra bite.

In 1561, when he must have been close on seventy years of age, he settled in ' Golden Goa,' the adjective being due to the splendour of the viceregal appointments, and two years later he published his *Colloquies on the Drugs of India*, a work written in the form of dialogues between Hellenists and Arabian physicians. It comprises very full accounts of important *materiœ medicœ*, interspersed and embellished with anthropological notes on the races of the people, their history, creeds, manners and customs. This work obtained wide popularity and was translated into Castilian, Italian and Latin, passing through several editions, and for some years was in fact the only work on tropical medicine available to Europeans. Some thirty-five years elapsed before George Watson's work—so far as we are aware the earliest work on the diseases of warm climates to be written in English—on *The Care of the Sick in Remote Regions*, was published in London in 1598.

The Portuguese were the earliest colonizers of the tropics and it is only natural that their physicians should be in the forefront of tropical practitioners and authors. It was Aleixo da Abron who in 1623, in a work published in Lisbon, gave the earliest known

description of the *Mal de Loanda*, or what we now know as African trypanosomiasis, or sleeping sickness. In short, Portuguese writers, not all of them physicians, may be said to have initiated the study of tropical diseases; next to them came the Dutch in the East Indies, and then the British, French, German, Italian and American investigators.

WILLIAM CRAWFORD GORGAS
(1854-1920)

William Crawford Gorgas was born at Toulminville, Mobile, Alabama, on the 3rd October, 1854. His father was General Josiah Gorgas and his mother, Amelia Gayle, was the daughter of the Governor of Alabama. It is strange how intimately this family was connected with yellow fever, the prevention of which was also the basis of much of Gorgas's fame. Josiah Gorgas was in the Mexican War and present at the siege of Vera Cruz where it was recorded of the American troops that " nearly all have been sick and they have died by the hundreds " of yellow fever. In 1853 Mobile, Alabama, was attacked by one of the worst epidemics on record which had ravaged the West Indies and the Gulf States, Alabama severely, and Mobile in particular. At that time a common name for the disease was the ' Yellow Breeze ' in the belief that it was wind-borne. Others were of the opinion that it was carried in oranges and bananas or that these fruits were the actual cause, and their importation was accordingly forbidden and cargoes of them were destroyed.

At the birth of William Gorgas his mother was attended by Dr. Josiah Nott, who was the first to incriminate the mosquito in yellow fever (see Yellow Fever). There is no need to dwell on Gorgas's youth. He appears to have lived the life of a normal healthy lad, enjoying outdoor recreations and it was his ambition to enter the army as a combatant. Of the many stories of his boyhood the following is perhaps worthy of note. He devoured eagerly all books dealing with the army and military life and his mother had remarked with joy and comfort his somewhat sudden but ardent devotion to bible-reading, as fond mothers do at certain times of their children's lives. The boy would lie on the floor absorbed in this occupation. Her joy was a little restrained, however, when she discovered that what held her son's breathless attention was the wars of the Israelites and the combatant passages of the Old Testament.

He moved as a boy from place to place with his parents and at the age of seven heard the guns from Fort Sumtor and during

the ensuing years he was to observe many of the horrors of war. In 1875 he set himself to study for the Bar but found reading law a wearisome task and gave it up after a year and again turned to the idea of a military career. By this time he was twenty-one years of age, too old to enter the Military Academy; he therefore resolved to take up medicine and in 1876 entered Bellevue Medical College, New York City, and having graduated he, in 1880, at the age of twenty-five and a half, was commissioned in the Medical Department of the United States Army, thus realizing part of his ambition—military service. For the first twenty years he lived the usual life of an Army surgeon in one station after another and these call for no special mention except for one incident which had an influence on his subsequent work in connection with yellow fever. Soon after he entered the Army Medical Service he was sent by the Chief Surgeon for duty at Fort Brown, Texas. At the request for help from the post surgeon, Major Haffersett, the Chief Surgeon when detailing Gorgas wrote : " I am sending you the most progressive young surgeon under ·my command." To Gorgas was ascribed the general duties at the new station and he was given strict orders not to visit the yellow fever ward of the hospital. As a young man of enterprise and as a ' progressive young surgeon ' he naturally disobeyed orders and in consequence was formally put under arrest and made to take up his quarters in the infected part of the garrison. After release from arrest, for he was needed for duty, he had to remain in the garrison and actually attended yellow-fever patients until he himself caught the infection.

The story is quite a romantic one. His chief, Colonel Lyster, summoned him to see his daughter, Doughty, who had early that morning had ‘a rigor, the onset of yellow fever. Her attack was a severe one and on the fifth day the doctors gave up hope and Dr. Melon, pointing to a grave which had been dug, said that it was for Miss Lyster and asked whether Gorgas would take the funeral and read the service. Gorgas agreed, but the patient held her own and Gorgas went down with the disease. She had a cardiac complication which kept her in bed until the fifteenth day of illness whereas Gorgas's attack was uneventful, and they entered convalescence the same day. Mutual affection deepened and they were later married.

Gorgas's recovery from the fever rendered him immune for life and enabled him for the future to attend cases and engage in yellow-fever work with impunity ; the experience at Fort Brown proved thus a blessing in disguise.

PLATE VIII.

WILLIAM CRAWFORD GORGAS.
1854—1920.

[Photograph kindly lent by the London School of Hygiene and Tropical Medicine
[By permission of the Dean, Sir Wilson Jameson

We may skip the intervening years to 1898 when, as a major during the Spanish-American War, he was in charge of the yellow-fever camp at Siboney and on his advice the little town was burned with all the medical and quartermaster's supplies—a woeful waste, but deemed justifiable on the knowledge at that time. The same year Gorgas became Chief Sanitary Officer, Havana. Much of what follows has already been referred to in the chapters on Yellow Fever.

When Gorgas started to clean up Havana the situation as regards yellow fever was not serious and deaths from it were few, the reason being that the bulk of the population were natives and immune; the return of the Army to Spain had *ipso facto* evacuated the town of much of the susceptible element. Deaths, it is true, were many, but due to dysentery and enteric fever and malaria, particularly the two former, for the city was little better than a huge cesspool. Gorgas, as we have noted (see Yellow Fever), shared at that time the general opinion that yellow fever was a ' filth disease ' and was confident that a thorough clean-up of the city would get rid of the disease. Consequently it was cleaned; private houses, bakeries, butchers' shops, hotels, cafés, stores, not a building was overlooked and Havana became " as cleanly as Fifth Avenue." New drainage was installed, refuse disposed of, stable floors cemented. Typhoid and dysentery almost. disappeared but to the chagrin of the sanitarians deaths from yellow fever began to increase. Cessation of the war in 1899 stimulated immigration and in the following year 25,000 are said to have visited Havana, nearly all non-immune Spaniards from the mother-country. Moreover, as those who had been most irked by the great clean-up were not slow to note and naturally to impress upon Gorgas, in case he should miss it, the disease was more rife in the cleaned-up dwellings and among the better-class population than in the quarters of the poor. The reason, as we understand now, was that the poorer classes were the more or less immune natives, those in the better quarters were the susceptible immigrant visitors. Now came a time of tragedy. In the autumn three prominent officers died of yellow fever, one of them the Military Governor of the City. Another victim was the Chief Commissary of the Army. The widow of the latter in a paroxysm of grief and with the desire to take the infection threw herself on her husband's body and soiled herself with the black vomit. Failing to acquire the infection she committed suicide, shooting herself. Also a member of the General's staff who attended the funeral died of yellow fever within a week.

Dr. Carlos Finlay had watched the cleaning up of the city with no little interest and some scepticism, for it afforded an opportunity for testing the theory of mosquito transmission in which he had believed since his communication to the Medical Congress at Washington in 1881 (see Yellow Fever and Life of Carlos Finlay). Finlay, the ' beloved physician ' of Havana, and Gorgas were friends. The situation as regards yellow fever becoming more and more serious, desperate almost, the Surgeon-General, Sternberg, at Washington appointed a Commission to visit Cuba and investigate the whole vexed question. Members of this Commission were Walter Reed as head, James Carroll, Jesse Lazear and Aristides Agramonte. Lazear was at that time stationed in Cuba and Agramonte was a Cuban born.

We may interpolate here a few words on the work of Dr. Henry R. Carter of the American Public Health Service, not that a ' few words ' can do justice to his work but because his epidemiological conclusions arrived at as the result of acute observation had no little bearing on the work of the Commission. In 1899 Carter had sent to a medical journal a communication which comprised an elaborate study of yellow fever in houses. This paper was unfortunately rejected by reason of its length. Carter had been for years a quarantine officer and he had observed that when a case of yellow fever occurred on board ship, others, in spite of close association and contact in a crowded forecastle, were not attacked until the lapse of a considerable interval, and consequently he concluded that the disease is not contracted from the environment of a patient for some time after he became sick in that environment. Failure on Finlay's part to appreciate the importance, the significance, of this it was that prevented him from establishing his belief as a basic fact. In 1898 Carter was studying an outbreak of the disease in Mississippi and noted down the dates of origin of cases among contacts and found that those who were taken ill were such as had visited the house of the patient some 12–14 days after the onset of his symptoms and not such as had visited there only in the early days of the illness. This interval Carter named the " period of extrinsic incubation."

The conception appeared to be quite reasonable, the question was how to test it. The first experiments failed because Carroll and Lazear ignored this period of extrinsic incubation. Carroll, bitten by an infected mosquito a few days after it had fed on a yellow-fever patient, remained unaffected. Later (see Life of Carroll) he allowed himself to be bitten by an infected and infective (*i.e.* twelve days after the infecting feed) mosquito and he in due

time passed through a severe attack. Reed, who was at the time in Washington, then returned to Cuba and planned the classic experiments at Camp Lazear which have been detailed (see Yellow Fever). As the result of these he was able to prove that a patient was infective during the first three days of illness and that for a second case to occur the subject must be bitten by a mosquito which had fed on a patient during the first three days and that an interval of ten to fourteen days must have elapsed, during which the infected mosquito was harmless.

Up to this point the fact that Aëdes could transmit the infection had been proved; the next question to arise was " Is this the *only*, or even the *usual* way ? " This was the problem presented to Gorgas and he set about it in the following way, arguing that if due solely to the mosquito, yellow fever would disappear on elimination of that insect—a sound argument in theory but presenting enormous difficulties in execution. The mosquitoes were present in Havana in countless numbers in every street, every alley-way, every house, nook and cranny. On one occasion, it is said, Gorgas was discussing the ' theory ' and plan of campaign with a board of fifteen doctors who were dubious if not actually sceptical, and a covered jar containing Aëdes was on the table. While the conclave was adducing reasons for non-acceptance of Reed's hypothesis, the covering of the jar happened to come off and, almost as one man, all leaped for the door, destroying the wire screening in their hasty exit. This reminds one of the anti-vaccinationists in an English town going, like Nicodemus, by night to have themselves vaccinated in a time of smallpox scare.

Gorgas argued that to prevent yellow fever the chain ' man-mosquito-man ' or ' patient-mosquito-non-immune ' must be severed somewhere. Since mosquitoes were so numerous it would be a far more difficult task, even if it were possible, to keep them away from the patient than to keep the patient from mosquitoes, that is, to isolate the patient in a screened room at the first sign of disease. Even then the task was far from easy, for many of the milder cases, who were equally infective and dangerous, would escape recognition or might not be thought worth notifying, especially perhaps children.

The idea was mooted of attempting to immunize the population by inoculation with infected mosquitoes—as Finlay had done years before with the Jesuit Fathers—on the analogy of variola vaccination. Seven persons were thus inoculated and three died of the disease. Fortunately, known infected mosquitoes maintained in the laboratory were few. Reed had one only, known

with respect as " Her Ladyship," which had infected many and was pampered to a degree. She had a home—a glass jar—all to herself on a table in a sunshiny room, with abundant moisture, and the air of it kept at an optimum temperature by means of an oil-stove specially imported for the purpose from the United States. One morning at daybreak she was discovered with a wing caught in the mosquito-netting. How long she had been in this plight was not known, but she seemed to be moribund. Dr. Gorgas, Dr. Reed and Dr. John Ross were summoned and a consultation was held. The patient was gently liberated and laid upon a soft bed of cotton and the stove heated up, but naught availed and at 9 a.m. she passed away attended by more doctors than any human patient in Havana. Her demise was a heavy blow to the Health Department, a blow softened, however, when they heard of the deaths among the inoculated and were forced to conclude that attempts at immunization by such means was a hazardous procedure.

Aëdes, fortunately, was not so difficult to deal with as Anopheles or Culex, as it is more particular and selective in its ovipositing sites, and the need was to attend to the household and its immediate environs, the domestic and artificial receptacles for water. Gorgas and his squad undertook a very thorough investigation and a record was made of every house and every container. In February (1901) the order went out that every case or suspected case of yellow fever was to be placed in a room with openings screened by wire gauze—that is, made mosquito-proof—and all mosquitoes in that and the neighbouring houses destroyed. Within a week or two Gorgas had a hundred men employed in clearing out breeding-places. After June strict quarantine was relaxed ; all cases had to be reported, the patient's house screened and a warning notice displayed outside. A guard was attached to each patient and it was his duty to report whether all the sanitary regulations were carried out. By September the disease was to all intents eradicated.

Gorgas's tact must have been unsurpassed for, though an easily provoked, excitable Latin race, the people themselves came to demand the sanitary measures he initiated. We need not record the intermediate steps, but state that whereas in 140 years, from 1762 to 1901, there had not been a day when yellow fever was not prevalent in Havana, and, in the decade preceding the American occupation, this disease had taken a toll of more than 500 lives yearly—in 1896 there were 1282 deaths and in 1900, the

year preceding the undertaking of Gorgas, 310—from March 1901, when Gorgas began his campaign, there were only five deaths, all in July and August. To complete the story, there was in 1905 the beginnings of an outbreak which were promptly checked by reinforcing Gorgas's methods again, and since then there have been no outbreaks. Gorgas was always careful to assign the chief, at least the primary, credit to Reed and his fellow-workers, as having proved Aëdes to be the vector.

Gorgas and the Panama Canal

Much of what follows has in substance been given in the chapter on the Panama Canal, but in a sketch of Gorgas's life—of which this project was the chief accomplishment—at the risk of even some ' vain repetition ' we cannot omit it.

Linking of the Pacific with the Atlantic had been one of civilization's dreams from the early years of the sixteenth century (1513) when Balboa traversed the isthmus and first saw the Pacific. The idea, in project, appeared to be so simple, cutting a waterway through a mere forty miles of land. Yet the greatest engineering authorities of Europe, men who had had experience in the successful construction of a canal at Suez considerably longer, had after attempts extending over twenty years been compelled to give up the project, faced with failure, disaster and contumely.

As we have seen, when speaking of the Panama Canal, in 1904 America was ready to start. Yellow fever was known to be one of the worst, if not the worst of all, menaces and it was only natural that the man who had conquered this scourge in Havana should be selected to cope with the problem afresh in Panama. Gorgas with his innate thoroughness studied long the problems involved and, though in fact it helped little, visited Egypt to consider on the spot the sanitary problems of the Suez Canal. He knew that the French had lost heavily in their attempts, but the Company had naturally not published to the world the full tale of the failure.

In March 1904 Gorgas visited Panama; at that time the whole Zone was one sweltering miasma. In 1885 J. Anthony Froude wrote (see p. 371, above) :

> In all the world there is not perhaps now concentrated in any single spot so much swindling and villainy, so much foul disease, such a hideous dung-heap of physical and moral abomination. The isthmus is a damp, tropical jungle, intensely hot, swarming with mosquitoes, snakes, alligators, scorpions and centipedes ; the home, even as Nature made it, of yellow fever, typhus and dysentery.

Manson spoke of Panama as a place where germs may flourish all the year round, because here is no cold season to destroy them.

Between Colon on the Atlantic side and Panama on the Pacific was a hopeless tangle of tropical vegetation, marshes whose depths had not yet been fathomed, black muddy soil and shifting sands, rivers which might rise as much as 20 feet in a few hours, and volcanic hills.

The vegetation was an impenetrable mass of palm trees, mangroves, creepers of all kinds . . . and a never-ending panorama of animal life. Chattering monkeys, shrill parrots, birds of the most variegated plumage filled the trees ; wild turkeys, wild boars and wild hogs swarmed the tall grass, and poisonous snakes, great lizards, tarantulas and all manner of reptile and insect life covered the oozy ground. This terrible place was not lacking in beauty ; all kinds of tropical flowers bloomed there eternally, and its orchids had led more than one venturesome collector to his doom. The intense thunder and lightning storms that frequently illuminated the darkness, the showers of rain that constantly swept down upon it—huge masses of water that for the time obliterated the landscape—also had their own element of grandeur. But the general impression was one of dank terror.

Dr. Porras, a former President of the Panama Republic, said of the days of his youth :

I can still remember, and it seems to me a horrible nightmare when, on my way to Bogotá to finish my studies, I found it necessary to spend a night in Colon. Sleep during that night was impossible for me because of the constant tormenting bites of the mosquitoes . . . tormentors so numerous [some allowance must be made for nocturnal exaggeration of his discomforts] that by clutching at the apparently empty air I caught handful after handful. . . . On every hand one encountered well-beloved friends hastening home in the grip of malarial chills or some equally pernicious fever. . . . Those days have passed never to return and our tropical home has become one of the world's health resorts.

It was a common saying that there are two seasons at Panama ; first, the wet season from mid-April to mid-December when people die in three or four days from yellow fever ; and next, the dry or so-called healthful season when they die in 24–36 hours from pernicious fever. A journalist wrote in 1888 :

Since the advent of de Lesseps' canal men on the 28th February, 1881, thousands upon thousands have been buried here [i.e. at Monkey Hill, a burial place near Colon]. During two seasons of epidemic it is said that the burials averaged from thirty to forty a day and that for weeks together.

A not unusual sight during the period 1881–8, when the French work was going on, was to see a ship at anchor in Colon harbour

without a living soul on board, all the crew having fallen victims to yellow fever. In one month, October 1884, there were 654 deaths. Had the sickness of the French period been the same in the American there would have been some 13,000 constantly in hospital and a death-rate between 3000 and 4000 annually for the ten years taken by the Americans in the construction.

As in Havana, so in Panama, when Gorgas made his preliminary survey there was little or no yellow fever—there were few strangers, non-immunes, in the Canal Zone. By June 1904 there was a small personnel at work, namely W. C. Gorgas, J. L. le Prince, H. R. Carter, J. Ross, L. Balch, L. A. LaGarde, J. Turtle and Miss Hibbard, the head-nurse, but they had not been able to obtain even the most necessary supplies and help ; there were no men for general sanitation duties and all requests for them were met with the reply, " Oh ! get a few niggers." There was no sanitary force, little money and no official backing.

Reed's conclusions from the Commission's work in Havana had been accepted by tropical workers all the world over and Gorgas's success there had convinced sanitarians of the soundness of the application of measures based thereon, nevertheless they seem to have failed to penetrate the non-medical official minds. Thus, the head of the Commission entrusted with the work of the Canal was Admiral J. G. Walker who was convinced that the French failure was due to dishonesty, mismanagement and waste. Economy, therefore, was in the forefront with him and to

waste good American dollars on a group of insane enthusiasts who spent their time chasing mosquitoes through the Panama jungle seemed to him the very height of folly. Even the French in their wildest moments had never done anything so bad as that.

Requisitions made by the health and sanitation sections were, therefore, either ignored or refused, or, if acceded to, were granted grudgingly, niggardly and partially only. Gorgas tried in Washington for hours to talk him over to his views but without success. He was as dogmatic on medical matters as executive officers generally all the world over. He took the line that " Everyone knows what causes yellow fever ; it was not mosquitoes, it was filth and dirt." General G. W. Davis, the first Governor of the Cabal Zone, was equally impervious. " Sanitation," he would say, " sanitation ! What has that to do with digging the Canal ? Spending a dollar on sanitation is as good as throwing it into the Bay. It is for your good, Gorgas, I say this. You have harped on the mosquito idea till it has become an obsession and your

assistants have caught it too. Do, for Goodness' sake, get it out of your head. Yellow fever, as we all know, is caused by filth.''

Though not fearing mosquitoes, the members of the Canal Commission had a wholesome dread of the yellow fever and spent most of their time at Washington. How different from the Havana experience where the Governor, General Wood, backed up and co-operated with Gorgas in every possible way.

In November came Nemesis ! During the preceding months there had been a case or two only, now they began to increase in Panama, Colon and the villages between, and in a short time an epidemic was in progress. Panic set in and office men, engineers, labourers, all had but one end in view, to bolt for home and safety, but there was a serious obstacle—lack of transport. The project was tottering on the brink of failure just like that of the French ; in fact, the fate of this vast undertaking might, in 1905, be said to have rested in the hands of one man, Gorgas.

The water-supply of Panama and Colon was rain which had to be stored in receptacles close to the houses for accessibility, receptacles ideal for the breeding of Aëdes. Replacement of such a supply by a piped service had been followed by elimination of yellow fever from certain northern cities—Philadelphia, Boston, New York and others—and Gorgas saw that the domestic receptacles must be done away with or rendered safe from mosquitoes. This was driven home by a small outbreak on board the cruiser *Boston* then in the harbour. A party was given on board on New Year's Eve, 1904–05, and among the guests was an ambulant case of yellow fever. Two weeks later six of the ship's company were stricken with the disease. Mosquitoes were plentiful on the ship and they were found to be breeding in a pan of water outside the cook's quarters which was thick ' like a purée ' with larvæ.

The panic caused by this outbreak gave Gorgas his chance. A law was passed making the harbouring of mosquito larvæ on private premises punishable by a fine of 5 dollars. The city was divided into districts each under supervision of an inspector. Removal of domestic water receptacles forced the mosquitoes to seek for fresh places for oviposition. They found them in the large-leafed vegetation, in crevices of wayside stones, in thrown-out tins, in holy-water stoups in the churches. All these could not be dealt with in a short space of time, so traps were set—basins of clean water in selected spots. The insects returned to their former ways, regarding the old houses as swept and garnished, and they laid eggs in abundance. The basins were emptied, eggs

destroyed and fresh water supplied. This measure, supplemented, of course, by removal of pans, water-jars, barrels, and cleaning of yards, proved effectual. At the same time all the patients notified were placed in screened dwellings.

One great difficulty, perhaps the greatest, was to keep under control the plant life which in marshy places and near the water's edge would spring up in a night and contain enough water for abundant mosquito breeding. The Sanitary Staff was equipped with an apparatus which would give a powerful blast of burning petrol and destroy the roots of the undergrowth. Crab-holes were filled in; railway trains crossing the Isthmus were meticulously examined for straggling mosquitoes. If a man telephoned to the Sanitary Squad of his district that a mosquito had been found in his residence, in a few minutes a truck would arrive with a sanitary inspector and four or five labourers who would go through the house peering for mosquitoes, and having flashlights for investigating dark corners. Any mosquitoes found were caught in test-tubes, chloroformed and examined for determination of the genus; thus it would be known whether they had bred in the house or had come from without and further measures would follow on the decision.

Then came another blow and many patients admitted for other diseases to the Ancon Hospital developed yellow fever. This came to such a pitch that patients recommended for admission expressed their preference to die at home. At this hospital ants also were troublesome and, as is customary in tropical countries, to protect food from their ravages the feet of the food-safe were kept in small pans or cups containing water. Examination of these showed them to be the breeding sites of mosquitoes, and the removal of them and screening of the buildings put an end to hospital-acquired yellow fever. In September 1906 the last fatal case of the disease was subjected to autopsy and Gorgas was able to boast—had he been of a boastful nature—that six months' strenuous work had got rid of a scourge which had afflicted the district for four centuries.

The course of the campaign had not been quite so smooth as the foregoing would lead us to suppose. As the result of adverse reports on Gorgas from members of the Commission—the laity —at Washington, the Secretary for War visited the area and as the result of his inspection expressed his concurrence with the Commission that Gorgas was a failure, that his retention was endangering the success of the scheme and that he ought to be replaced.

Early in 1906 Dr. Reed—Charles A. L. Reed, not the Walter Reed of Havana fame ; he had died in 1902 (see Life of Walter Reed)—was sent by the American Medical Association of which he had formerly been President, to investigate quietly and report. He remained three weeks, examined into everything, while withholding the purport of his visit.[1]

On his return Dr. Reed published the result of his investigations—a crushing indictment of the Walker Commission, pointing out the folly of making a man of Colonel Gorgas's distinction and eminence, the leading authority on sanitation and yellow fever, subordinate to a number of others, themselves subordinate, none of whom knew anything of the scientific aspect of the questions at issue. He instanced the difficulty in getting supplies and the needless delay. He quoted the routine procedure which certainly strikes one as ludicrous ; thus : If the Superintendent of the Ancon Hospital makes a requisition for supplies, he must make it on a certain form, take it for approval first to the Chief Sanitary Officer, then to the Governor of the Zone and then to the Chief Disbursing Officer. Thence it is sent to the Commission at Washington who relegate it to a special committee-man, who in time sends it back to the Commission. If it is allowed to go through, bids are advertised for and award is made. The requisition is then filed under the supervision of a purchasing agent who, by the way, has no knowledge whatever of the character and quality of medical and surgical supplies. The material is then shipped to the Isthmus consigned to the Chief of the Bureau of Materials and Supplies who notifies the Disbursing Officer. The latter notifies Colonel Gorgas who in turn informs the Superintendent of the hospital and he applies to the quartermaster for transportation. It was a common experience for part only of the

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[1] In this connection the author's experience was once very similar. When investigating the Vomiting Sickness of Jamaica he reported his findings that it was due to a form of food poisoning and had nothing whatever to do with yellow fever as Potter had reported two years before (1913). One day a Surgeon-General (S. G. Blew) from Washington called at the laboratory and had a long talk on disease in Jamaica and particularly the Vomiting Sickness. I had the privilege of showing him histories of cases, descriptions of post-mortem findings and sections of tissues. When he was leaving he shook me by the hand and said that he had been sent over from Washington because there was a⁻suspicion that the authorities of Jamaica, with my connivance, were concealing the existence of yellow fever under the name of Vomiting Sickness. He had been in the island for some time making inquiries secretly and had concluded to come and have a talk with me. He expressed his perfect satisfaction and no one could have made a kinder *amende honorable* than he did. Colonel Gorgas chuckled with glee when he and the author met some two years later and the latter recounted the circumstances.—H. H. S.

demand to be supplied even after all this circumlocution and peregrination.

Dr. Reed's report did much good.   President Roosevelt, a man of action, on hearing of this mode of procedure at once swept it all away.   A new Governor of the Zone, by name Shonts, was appointed in March 1905, when yellow fever still existed.   He made up his mind to replace Gorgas and appointed an old friend, an osteopath, as ideally suitable for the post of Chief Sanitary Officer.   Mr. Taft, the Secretary for War, approved but the President withheld his consent until he had consulted Professor Welch and later Lambert.   Shonts had reported that " the smells of Panama are as bad as ever."   [This was the time when ' smells ' were still believed to cause disease *per se*.]   Lambert told the President plainly, " You can back the old idea and clean out the smells and see your men die of malaria and yellow fever, or you can first clear up the puddles and kill the mosquitoes and then clean up the place by ordinary sanitary methods."   He told of 500 young engineers brought from France, none of whom lived to draw his first month's pay after being set to work in the swamps. The upshot was that President Roosevelt paid a personal visit and not only retained Gorgas but made him a member of the Commission.

In 1908 Colonel G. W. Goethals became Chairman and Chief Engineer and made no secret of his contempt for Gorgas.   It is reported that on one occasion he said : " Do you know, Gorgas, that every mosquito you kill costs the United States Government ten dollars ? "—" But just think, Colonel Goethals," replied Gorgas, " one of these ten dollar mosquitoes might bite you, and what a loss that would be to the country."

The yellow-fever problem having been solved there remained another, less fatal perhaps, less dramatically fatal at all events, but even more difficult, namely *malaria* ; for, whereas Aëdes breeds almost entirely in or close to dwellings and in comparatively pure water, Anopheles will breed almost anywhere, in marsh, pond, or mud-puddle, and its eradication entails draining of swamps, filling in of ponds, levelling roads, cutting grass and bush, constructing properly graded ditches, and so on.   In Panama, besides the natural breeding-places, the canal construction work constantly created fresh ones.   Every hole made by the steam shovel would soon contain water and become a site for Anopheles to oviposit ; the bottom of the canal was irregular, almost honeycombed with holes, and every footprint of horse and cattle was a potential

breeding site. The jungle portion of the 500 square miles of the Zone was uninhabited and therefore negligible for the time being. Gorgas's aim was to keep an area 200 yards wide round any inhabited part free from Anopheles. To that end all swamps within such a radius were drained (it is said that there were 8,000,000 feet of ditches), all undergrowth cut and grass was limited to a foot in height, to prevent mosquitoes lurking at the edges of lakes, ponds and watercourses. Drip-pans were installed for the steady dropping of oil over the surface of streams, and natural enemies of mosquitoes or their larvæ were introduced. The result was that, whereas in 1906 more than 40 per cent. of the workmen were admitted each month to the malaria wards of the hospitals, by 1913 this figure had been reduced to under 10 per cent. The work, there can be no doubt, would have been even more successful had not Colonel Goethals insisted on transferring the construction of drains and the cutting of grass, both sanitary measures of the utmost importance, from the medical and Sanitary Department to that of the Quartermaster.

Apart from the main hospitals, the Ancon Hospital on the Pacific side and Colon Hospital at the Northern end, emergency hospitals, each with thirty-six beds, were established along the line. The chief of the hospital division was John W. Ross of the United States Navy who had been associated with Gorgas for some years, at Fort Barrancas and at Havana, and they worked well together.

The foregoing brief sketch is sufficient to show, though perhaps inadequately, that the building of the Panama Canal was more than a triumph of engineering and of sanitation, it was a triumph also of character. In the face of obstruction, of active opposition, of difficulties of many kinds Gorgas's supreme patience, resolution and tact had made the final goal attainable. By the time the Canal was completed, in 1914, the death-rate at Panama from all diseases was below that of any American city or State. The general death-rate of the United States in 1914 was 14·1 per mille ; of individual States three only had a rate below 10, namely Washington 9·5, Minnesota 9·4, and Nebraska 9·2 ; that of the Canal Zone was only 6·2 per mille.

Leaving on one side the effect of the Canal on the movement of peoples and the world's commerce, as having no concern with our present purpose, the successful sanitation of the Isthmus, as Gorgas used to say, meant " a revolution in human history, for

it throws over the hitherto accepted truth that white men could not live in the tropics." The enervating effects of tropical climates have been dwelt on even to prolixity in the past years, but at the time of the opening of the Canal the workers were healthy and their children seemed vigorous. Why should not other areas, many of them vast in extent and hardly occupied at all, such as the Valleys of the Amazon, the Orinoco, the Congo, the Nile, support nations of white men ? If the causes of disease were removed these places might in-very truth become gardens. This was the meaning behind the Canal as Gorgas saw it.

Of Gorgas's other work we cannot speak in detail. He was now sixty years of age and much of that time had been passed in unhealthy environments. Reports had been coming for the preceding two years of the terrible mortality from pneumonia, a 30 per cent. fatality rate, among the Rand negroes in South Africa. When the Canal work started pneumonia was as destructive to the negro as yellow fever to the white population, so that this was not altogether a new problem to Gorgas. The huts of the negroes were relics of the days of French occupation, were badly constructed and leaky ; the labourers were too poor to afford more than one set of clothing and in this they worked and sweated in the heat, were soaked to the skin in the rains, and in this they retired to their cabins for rest, and their food was deficient. So many died that there was a fear that the West Indian authorities might prohibit their being recruited. By segregating those attacked, by putting an end to overcrowding, by improving their dwellings and their food Gorgas succeeded in eradicating pneumonia in epidemic form and established a contented and prosperous community in place of a sickly and depressed population dwelling in broken-down settlements.

Invited to visit Africa and advise, Gorgas accepted and left for England in the autumn of 1913 and sailed thence for Capetown. With Major Noble and Dr. Samuel Darling he made a tour of inspection and found that the custom was for labourers to be enrolled at Inhambane to work in the mines and to be brought thence by ship and rail to Rosanna Garcia and kept there until some 1200 were got together. In their scanty clothing they would be taken to the high veldt, 5000–6000 feet above sea-level.

The crowding on the ship, at the collecting station and in the train afforded ample opportunity for infection and on arrival there were always a few ill with pneumonia. In the mines they were chilled on emerging from the heat and moisture below to the open

air above and latent infection became lighted up.   In the barracks close contact again favoured conveyance of infection.

Gorgas's investigations were brought to an end in the following January by a strike on the mines, but before he left he handed to the Transvaal Chamber of Mines his report on the causes and his recommendations for prevention.   Many of these were subsequently made effective and, though they were not novel, the results exceeded expectations and within four years the mortality from pneumonia fell to about three per thousand and that from all other diseases to six per thousand.   Dr. Orenstein, in commenting on this, says that prophylactic inoculation has been stated to be the great declining factor.   It certainly played a part, but it must not be forgotten that it had been employed in some mines before 1913, and the fact that the mortality from other diseases—in which, of course, inoculation against pneumonia could play no part—was reduced from 13 to 6 per mille is clear refutation of that belief.

On his return to London in 1914 Gorgas was received with honour.   Oxford University conferred on him an honorary D.Sc., and Dr. A. D. Godley in the course of his speech as Public Orator said :

Those are most to be honoured by us who have increased knowledge and thereby promoted the welfare of the world. . . . It is a fine thing to have the scientific knowledge which can cure disease ; but there is a still finer if more dangerous task for those who can extirpate the causes from which disease springs.   It is such men who destroy the seeds of death which are bred in swamps, risking their health and even their lives to save their fellows.

The eminent American whom you see to-day has . . . fought in the forefront of the battle.   His achievements are too numerous for me to relate in detail.   Suffice it to say that it is he who cleansed Havana ; it is he who put fever and pestilence to flight in the Isthmus of Panama, and made possible the long-thwarted construction of the great interoceanic waterway ; it is he who has recently improved the sanitary conditions in the South African mines. . . .

The result has been an amelioration of the conditions of human life in plague-haunted districts, where once " in silent fear the helpless healer stood," and it is now possible to live in comfort and to work with advantage.   There can be no better example to those

" Whose skill hath served the human lot to raise,
And won a name that endless ages praise."

Gorgas's achievements found a much wider application than Havana and Panama.   As a result of what he had done the Rockefeller International Health Board took up the question of yellow

fever in the Southern States and elsewhere. The importance of this must not be underestimated. The opening of the Panama Canal brought China and the Far East into close touch with the Gulf ports and history had shown abundantly how easily the infection had been introduced and spread by commerce. It would be terrible if the benefit of the shorter route entailed introduction of yellow fever into Hong Kong, Singapore, Colombo and other places east where it had never before been known, for Aëdes abounds in all and the countries are inhabited entirely by non-immunes ; hence, if the virus were once introduced it is probable, nay certain, that there would be deaths by the thousand. The best way to deal with the menace was to eliminate the evil at its source. Consequently, in May 1915 the International Health Board resolved to enter the field of yellow-fever control and Gorgas was invited to visit suspected countries, seeking out the hiding-places and preparing material and data for a comprehensive campaign. This occupied several months. Gorgas and his party, which included Dr. Carter and Juan Guiteras, an associate of the old Havana days, visited Ecuador, Peru, Colombia, Venezuela, Brazil, Mexico and several of the Central American States. Here again his infinite tact came into play for the Latin-American peoples are proud and their sensibilities readily wounded, yet practically the whole of Central and South America was brought within the sphere of action of the Board.

Of his work in the Great War of 1914–18, after America entered into it, how he increased the original number (435) of regular Army Medical Officers and the 2000–2500 in the Medical Reserve Corps to over 32,000 medical officers in active service and more than 35,000 civilian doctors enrolled in the Medical Reserve Corps ; how he acquired an enlisted personnel of 250,000 men and 22,000 nurses it is not for us to do more than mention, for, though a wonderful and fitting climax to a busy life, it has little or no concern with the history of tropical medicine.

Though at the time of the Armistice Gorgas was over sixty-four years of age he was still avid for fresh fields to conquer and within a month he accepted a commission from the Rockefeller Foundation to visit Guayaquil, Ecuador, to advise and assist in eradicating yellow fever. Soon afterwards Dr. M. E. Connor took charge of the work in this area and, following Gorgas's lines, had it practically clear in six months.

Meanwhile suspicious rumours were afoot that yellow fever had broken out in the vast district situated about Senegal and the

Belgian Congo. A British Commission had carried out some investigations and their report appeared to confirm the rumour. In spite of his sixty-six years General Gorgas accepted a proposal that he should go there himself to confirm or dispel the rumour —at least to obtain information of a more definite character. He sailed in May 1920 for London to be present at the International Hygiene Congress to be held in Brussels in June, where the award of the Harbin Gold Medal was to be bestowed on him by the King of the Belgians. On returning to London he was taken ill and brought to the Queen Alexandra Military Hospital, Millbank. While there he was visited by His Majesty, King George V, and invested with the insignia of Knight Commander of the Most Distinguished Order of St. Michael and St. George, which he was too unwell to go to Buckingham Palace to receive. Early in July, on the 3rd, he passed away. His funeral service was held in St. Paul's Cathedral, after which his body was taken to America and, after lying in state for four days at Washington, he was buried on one of the most beautiful slopes of Arlington.

The Commission to West Africa of which Gorgas was to have been the head duly visited the country, J. Guiteras taking Gorgas's place. In the report it is stated that they were not able to discover any cases of yellow fever and.they were struck by the absence of extreme heat and the hordes of mosquitoes which characterize yellow fever localities in South America. They were of opinion that the disease had but a small footing in West Africa and that it might have actually disappeared, the last epidemic having occurred in 1910–12. This has been shown by records of more recent years to have been rather too optimistic a view.

The following words may be quoted from an article which appeared in the *Lancet*, as a tribute to Gorgas :

He was the best known and most uniformly successful medical administrator, not of his age alone but of any age. . . . No sooner were discoveries made tracing an endemic disease to a source removable. by rigid hygienic measures than the services of this master-administrator were requisitioned to the farthest quarter of the globe to carry out such measures. And as if by magic—black magic, as it appeared to the slovenly, careless inhabitant ; white magic to the admiring world outside—the areas were cleansed and freed. But there was no magic other than that wielded by a strong personality with only one idea in mind—the speedy accomplishment of the work of the moment. Havana, Panama, the Transvaal, the endemic regions of yellow fever in South America, are only the best known sites of his activities.

The reputation of Gorgas as a scientist has been challenged in

certain quarters, in view of the fact that he was not responsible for the actual discoveries without which his work could not have been done. For this he needs no defence. Science and art are at their greatest when they join hands, and the man who acts as a link between discovery and its application needs a combination of qualities as rare as those of the pure investigator.

The following sonnet was written on Gorgas by Clarence Edwin Flynn.

> Into the fetid swamps of Panama
> A little grey-haired man with gleaming eye
> Went, drained them true to sanitation's law,
> And let the scourge of yellow fever die.
> The Stegomyia searched the humid plain,
> His [1] home through all the centuries of yore,
> But looked for his old habitat in vain.
> The dredge had banished it for evermore.
> Simple it was, when one knew what to do,
> As Gorgas did, and how to do it well.
> Now the long reaches of the ages through,
> Life will abide where Death was wont to dwell.
> Thanks to the Providence that sent him there,
> That modest little man with silver hair.

[1] 'Her' would have been truer to Science.

JESSE W. LAZEAR
(1866–1900)

Jesse Lazear was born in Baltimore on the 2nd May, 1866. After preliminary education at a private school in Washington, Pennsylvania, he studied at Johns Hopkins University and graduated in Arts in 1889 at the age of twenty-three years. He then moved to Columbia University where three years later, in 1892, he took his degree in Medicine and from then till 1894 worked at the Bellevue Hospital, New York, and here he for the first time succeeded in isolating the gonococcus from the blood of a patient suffering from ulcerative endocarditis.

The next year he spent in Europe, studying at the Pasteur Institute in Paris and elsewhere, and on his return to America was appointed bacteriologist and ' assistant in clinical microscopy ' or Assistant Resident Physician at his old University, Johns Hopkins.

Lazear also did considerable work on the structure of the malaria plasmodium and in conjunction with Woolley and Thayer confirmed the findings of Ross and the Italians on its development in the mosquito. He also had some experience of health conditions in Cuba.

After three years spent in problems of research it was but right and natural that he should be appointed a member of the American Yellow Fever Commission with Walter Reed at the head and James Carroll second in command. Lazear had been working, as has been stated above, for some months in Cuba before the rest of the Commission arrived in Havana and had already carried out several autopsies ; he had attempted hæmoculture but found nothing positive therefrom.

Soon after the arrival of Reed and Carroll he allowed an Aëdes mosquito, which had bitten a yellow-fever patient some days before, to feed upon his blood, but without result—evidently the interval had been too brief for the virus to develop. About a month later, on 13th September, when he was going round his ward in' Las Animas Hospital, a mosquito alighted on his hand and he allowed it to feed undisturbed, either not knowing or not

realizing that it was an Aëdes (Stegomyia). Five days later he had a chill, the first of several, and his blood proving negative for malaria parasites, he was removed to the yellow-fever isolation camp at Quemados. On the 21st black vomit set in and four days later he died, on the evening of the 25th September, 1900, at the early age of thirty-four years.

Lazear was buried in the Lindon Park Cemetery, Baltimore. There is a memorial tablet to his honour at the Johns Hopkins Hospital; on this his death is stated to have taken place on the 28th September. The site of the subsequent experimental work carried out by the Commission was known as Camp Lazear in honour and in memory of this martyr to science.

WILLIAM BOOG LEISHMAN
(1865-1926)

William Boog Leishman, the son of Dr. William Leishman who held the Chair of Medical Jurisprudence in Anderson's College and was Professor of Midwifery, Glasgow University, was born in Glasgow on the 6th November, 1865. Part of his pupilage was spent at Westminster School after which he entered Glasgow University as a student of Medicine and qualified there at the early age of twenty-one, in 1886, and immediately entered the Army Medical Service, being gazetted Surgeon in 1887. Early in his military career he was sent to India and, to the surprise of many of his colleagues and seniors, took with him a microscope. While in India he paid special attention to enteric fever and kala azar, and towards the end of his tour saw active service in the Waziristan Expedition of 1894-5. In 1897 he returned to England and was posted to the Victoria Hospital, Netley, as medical officer. Netley was at that time the Headquarters of the Army Medical School —afterwards transferred to Millbank as the Royal Army Medical College. Dr. (later Sir) Almroth Wright was then Professor of Pathology and Leishman gained experience under him and together they inaugurated inoculation against typhoid fever. He also assisted Wright in his work of antityphoid inoculation in the South African War (see below) and in opsonic investigations of the Staphylococcus and *Brucella melitensis*.

In 1900 Leishman was appointed Assistant Professor of Pathology in the Army Medical School in succession to Major (later Sir David) Semple. Soon afterwards he made his first original contribution to medical literature and to science by his method of staining blood for malaria and other parasites, whereby the two-stain Romanowsky method, as modified by Manson, was replaced by the simple process with a double-staining compound of methylene blue and eosin, known ever since as Leishman's stain and used all over the world.[1]

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[1] It is interesting to interpolate here a brief note on the history of the development of the so-called Romanowsky stains. The stain first came into use in 1890 and, because of the irregularity of results obtained with

PLATE IX.

SIR WILLIAM LEISHMAN.
1865—1926.

[Photograph kindly lent by the Leishman]

In 1901, when staining spleen smears from a soldier dying at
Netley of Dum-dum fever—kala azar—he observed certain bodies,
oval in shape, 2–3 microns in diameter, each with two chromatic
masses, one spherical and one rod-shaped (see Leishmaniasis).
He drew these and then waited for further cases to confirm his
findings.   In 1903 he published his account of them and this was
followed a few months later by a similar record by Donovan of
these bodies found by him independently in blood from the spleens
of kala azar patients, bodies called, therefore, Leishman-Donovan
bodies.   Rogers reported his success in cultivating them the follow-

it, solutions apparently identical giving now good, now bad preparations,
many modifications have from time to time been proposed.   These were
initiated as early as 1891 when Malachowski made a chemical analysis of
the stain and found that during the polychroming process the methylene
blue developed metachromatic dyes.   Even before Romanowsky, Bernth-
sen, in 1885 and subsequently, had shown that methylene blue when
oxidized became methylene azure, but little attention was paid to this
work for fifteen years when Michaelis and Ehrlich applied it to hæmatology.
Maurer in 1900 showed how the depth of the stain could be controlled by
using different proportions of eosin and alkaline methylene blue.

Meanwhile Unna, and later Nocht, concluded that the ' Rot aus Methy-
lenblau ' might be used to indicate the degree of polychroming or the
' ripeness ' of the stain.   Michaelis came to the conclusion that of the
many constituents of a polychrome stain, only two—methylene blue and
methylene azure—were of service for blood smears.   The next year a
further advance was made when Giemsa, working with Nocht, advocated
pure dyes which could be made into standardized solutions, in place of a
mixed stain of varying degrees of polychromatism and excluded methylene
violet, using pure methylene blue, methylene azure and eosin.   Giemsa
prepared from pure azure, Azure I, and Azure II a mixture of Azure I and
methylene blue in equal parts, and the stain called by his name consists
of separate solutions of Azure II and eosin mixed just before being required
for use.   His methods he did not reveal except to the chemist Grübler.
H. F. Harris in 1903 found that eosinate of polychrome methylene blue
was superior to the Giemsa stain.

Reuter in 1901 noted that a precipitate occurred when solutions of
eosin and alkaline methylene blue were mixed, and he prepared a stain
by filtering off this precipitate and dissolving it in alcohol.   Leishman's
modification consisted in employing methyl alcohol in place of ethyl alcohol
as a solvent.   In his paper in the *British Medical Journal* of 21st September,
1901, he gives minute details for its preparation—a powder of greenish
metallic lustre.   For use it is dissolved in a proportion of 0·15 per cent.
and the solvent fixes the film.   It has the further advantage that it does
not deteriorate on keeping.   The method surpasses that of Reuter in not
needing preliminary fixation of the film, in staining in five minutes in
place of two hours or more, and in not precipitating on the film when
ordinary care is taken.

We need only mention, without going into detail, subsequent develop-
ments such as Pappenhaim's ' panchrome ' stain, using toluidine blue,
methyl thionine, methylene azure and methylene violet, and MacNeal's
work in producing his tetrachrome stain and thus making available a
compound stain of fixed composition whose action can consequently be
controlled.

ing year and also described their passing through a flagellate stage in development. This caused Leishman to suggest the probability of an insect host and transmitter. The continuation of the story has been given in the chapter on Leishmaniasis and need not be repeated here.

Sir Almroth Wright having accepted the post of pathologist to St. Mary's Hospital, London, Leishman succeeded him as Professor at Netley and continued his researches on the preparation of anti-typhoid vaccine. In 1905 he was promoted Brevet Lieutenant-Colonel and for the next five or six years he spent what time he could spare from his teaching duties in research on the spirochætes of relapsing fever, in attempts to cultivate them and to distinguish the African-tick-transmitted form from the louse-borne variety and to determine in more detail their life-history. The outcome of these studies was published in his Horace Dobell Lectures delivered at the Royal College of Physicians in 1920.

To return to the subject of antityphoid vaccination. The results from its use in the South African War were very varied, some units reporting encouraging results, others finding it ineffectual. Nevertheless, although in the early stages the treatment had not been systematized, the morbidity among the uninoculated was to that among the inoculated in the proportion of 3·2 to 1. The poor results obtained in certain units has been explained by the suggestion that some, perhaps many, of the infections among them were not by *Bacterium typhosum*, but by one or other of the paratyphoids. The varying accounts of benefits accruing from the use of the vaccine led to its being temporarily suspended while a departmental Committee, with Dr. (later Sir Charles) Martin as Chairman, discussed the question of its cessation or continuance. The Committee decided that inoculation should be again employed, but as a voluntary measure. This would not find mention here except for the fact that other proposals were made for further investigation and experiment, and the supervision of these was entrusted to Leishman, himself a member of the Committee. The inquiry was directed to experiments on controlled inoculation and to determination of the best methods of preparing and administering the vaccine. Three years were spent in this research and the outcome was the production of the triple Typhoid-paratyphoid A and paratyphoid B (TAB) vaccine which, placed on a sound basis as the result of this work, was to prove so wonderful a prophylactic in the Great European War.

At the beginning of this war, in August 1914, only about 25 per cent. of the troops were inoculated prior to embarkation.

Enteric fever broke out and spread. By July 1915, largely owing to Leishman's efforts and advocacy, 95 per cent. of the men had received inoculation and by the end of the year a further 3 per cent. The prevalence and incidence of typhoid fever fell rapidly and by the end of 1915 was not a serious cause of loss of military strength. Had the rate been the same as in the South African War there would have been over half a million cases and more than 77,000 deaths, whereas in all the theatres of war the cases numbered only 20,139 and deaths 1191.

In the meantime Leishman was beginning to " bear his blushing honours thick upon him." In 1909 he had been knighted ; the following year he was elected a Fellow of the Royal Society, and in 1912 was Honorary Physician to His Majesty the King. In 1913 he gave up his pathological work at the Royal Army Medical College on being appointed Expert on Tropical Diseases to the Army Medical Advisory Board ; he was also an original member of the Medical Research Council and continued to serve on it for ten years. In 1914 he was elected a Fellow of the Royal College of Physicians of London. In October that year he crossed to France as Adviser on the staff of the Director-General of Medical Services with the Expeditionary Forces. He was Chairman of the Committee engaged in the investigation of Trench Fever. For his services he was created Companion of the Order of the Bath (Military) and was awarded the Legion of Honour (Third Class) by France, and by America the Distinguished Service Medal. In 1918 he returned to the War Office and took up the duties of the new Directorate of Pathology and Adviser in Tropical Diseases to the Director-General. This same year he was created Knight Commander of the Most Noble Order of St. Michael and St. George and given the rank of Major-General. He subsequently served on the Yellow Fever Commission of West Africa and as a member of the Medical and Sanitary Advisory Committee for Tropical Africa at the Colonial Office. He held his Directorate of Pathology till 1923 when he succeeded Sir John Goodwin as Director-General of the Army Medical Service, was promoted to the rank of Lieutenant-General and created Knight Commander of the Order of the Bath. He was also made a Grand Officer of the Legion of Honour by the French Government.

At one of his last public lectures, the Linacre Lecture, delivered in 1925, he sounded a warning against resting satisfied with work accomplished :

On the whole we are too much inclined to congratulate ourselves on the remarkable progress which has been made in tropical medicine during the last thirty years and to lay stress on what has been done rather than upon what remains to be done. . . . Accurate knowledge of the causation of disease, the diffusion of that knowledge and its utilization by an efficient health service have [in the case of the white man] made life in the tropics, at any rate in most places, almost as safe as at home. . . . Let us turn, however, to the other side, the case of the three hundred million of the native races for whom we are responsible. . . . Their condition in many countries is such as should give us cause for heart-searching and for the gravest disquietude. . . . The native, from the health point of view, is in many countries little, if at all, better off than he was before we accumulated the mass of knowledge from which the white man has benefited and is benefiting so greatly.

Tropical research has no reason to be ashamed of the amount of light which it has thrown on dark places, but it is only here and there that this knowledge has proved to be of such a nature that it can be readily, and above all economically, applied to the control of the disease in question on the scale required in practice. . . . The lines of approach are innumerable, and each disease has its own unsolved problems and its own difficulties.

Sir William Leishman was only sixty-one years old when he died, untimely, on the 2nd June, 1926, at Queen Alexandra Military Hospital, Millbank.

JAMES LIND
(1716–94)

Little is known of the details of the life of James Lind ; it is by his works that we know him. He is sometimes confused with another James Lind, also a physician and a contemporary (1736–1812) (see above, p. 31). The biographical facts can be summed up in a very few lines. Born in 1716 he joined the Naval Medical Service in 1739 at the age of twenty-three years and nearly all the next ten years were spent in the tropics, his service being on the Guinea Coast and in the West Indies. He took the M.D. degree at Edinburgh in 1748 and during the ensuing decade he lived and practised in that town. In 1758 he received the appointment of Physician to the Royal Naval Hospital at Haslar, a hospital with 1000 beds, and during his first two years there 5743 patients were admitted, one-fifth of them being cases of scurvy. The Channel Fleet would commonly arrive at Portsmouth with between 1000 and 2000 cases on board and during the Seven Years' War Lind had between 300 and 400 cases constantly under his care. Scurvy seems to us, now, an easy disease to diagnose, but in Lind's day the name was used to cover all sorts of conditions, even pleurisy, ague and hysteria. Engalenus, a Dutch physician, at the end of the sixteenth century had no difficulty, he said, in diagnosing it. " I diagnose the disease as soon as I place my hand on the pulse," and it is not surprising, therefore, that he found scurvy everywhere ; he attributed it to God's anger for man's sins.

Lind's *Treatise on Scurvy* and its treatment, published in 1753, was revolutionizing and marked an epoch. More will be said of this later. In 1757 a second work by him was published, entitled *On the Most Effectual Means of Preserving the Health of Seamen in the Royal Navy*. In 1768 he published a third work on *Diseases incidental to Hot Climates*.

Lind's reputation is based not only on these. In addition he made a study of typhus fever and recommended. to prevent the spread of the disease, bathing, change to clean clothes, the baking of lice-infested clothing—in short, delousing. He also introduced

portable soups and food in dry, powdered form into the Navy and in 1761 devised a method for rendering sea-water potable by distillation, though he was not the pioneer in this, as we have already seen.

His death took place on the 13th July, 1794, and he was buried at Porchester, in Hampshire, in the church of which there was put up a tablet to his memory.

Though he probably achieved more lasting good than any physician of his time, though seamen of all nationalities owe to his forethought, keenness and industry much of the benefits they received, he was awarded no honours in his lifetime, no honorary degrees, no election to the Fellowship of the Royal Society, no recognition of his work as did his contemporary, Sir John Pringle, the ' founder of Military Medicine.' The tablet in the church at Porchester is all, and that was a posthumous honour—in short, he shared the fate of many, of most, devotees to science.

But, if we are acquainted with few of the details of his personal life, we seem to know him well through his books and it will not be amiss to refer to these a little more minutely, for they were based on his personal experience.

The first was the *Treatise on Scurvy*, published in 1753, and in this he gives a good account transcribed from the journal of a Mr. Ives of the ship *Dragon* on which scurvy broke out, improved and again broke out, this sequence being repeated during 1743 and 1744 according as vegetables and fruits were obtainable or not. Lind's clinical experiments have been detailed in the chapter dealing with Scurvy (see Avitaminosis). As the whole fruit— lemons—might be difficult to obtain and, if obtainable, difficult to store, and, if stored, liable to spoil on board, Lind suggested and used with success ' depurated juice,' that is the juice concentrated by being heated in a water-bath—a punchbowl or earthenware basin wider at the top than the bottom, containing water kept near boiling-point.

Till Lind's time, though there were a few more enlightened on the dietetic causation of scurvy, the disease was attributed generally to intense cold, on the ground that it occurred in Greenland, and, fantastically, to laziness and lack of exercise, or debilitating illness, even fear and sorrow, by " relaxation of the tone of the animal fibres, weakening of digestion and stoppage of perspiration."

Sir Gilbert Blane and Thomas Trotter were enthusiastic followers of Lind and on a voyage to the East Indies a daily ration of lemon-juice was served to all the crew of the flagship and after

twenty-three weeks at sea they arrived at Madras and had not had a single case of scurvy on board.

Four years after his work on Scurvy there was published his book on the *Most Effectual Means of Preserving the Health of Seamen*. In the opening chapters of the present work we indicated the conditions under which sailors lived afloat in Lind's day— overcrowded in damp, dark, airless spaces, their food on long voyages consisting of " putrid beef, rancid pork, mouldy biscuits and flour " (Lind's own words) and " the number of seamen in time of war who die by shipwreck, capture, famine, fire and sword is but inconsiderable in respect of such as are destroyed by the ship diseases and by the usual maladies of intemperate climates." He showed how in times of war impressment brought on board the sick, the poor, the sweepings of streets and prisons to propagate contagion in overcrowded quarters, and how prevention depended on " clear and self-evident principles." His work deals not only with the men but with their quarters, clothing, cleanliness, food, airing by Hales's ventilators, the preventive use of ' bark ' for the crew when the vessel arrives at certain tropical places where " the air swarms with numberless insects and animalcules—a sure sign of a river's putrid and malignant disposition."

To prevent spread of disease on board he advocates well-aired berths, placed under the forecastle, so as to be protected from the rain, and with canvas screens around them. That this did not mean unalloyed comfort is clear, for he says that such a situation may be " too noisy and indeed sometimes noisesome from the Stench of the Hogs and Privies, or deemed improper as [near] the kitchen of the Ship, or otherwise thought incommodious from the wet and jolting Rebukes it meets with in stormy weather." If the sick are numerous enough to interfere with the working of the ship, the patients are to be removed to the gun-room.

There is but one objection that can well be made against this step, *viz.* the Inconvenience which may arise from it to the Officers who eat and sleep in that Part. But how trifling must this Objection appear . . . there are few Officers in the English Service who would not willingly quit their Habitation in the Gun-Room, for the Benefit and Preservation of the Men.

The air may be purified by fumes of camphorated vinegar, of pitch tar, or burning a small quantity of gunpowder, the last to be repeated as long as the operators can stand the smoke.

As regards Lind's third book, *Diseases incidental to Hot Climates*, published in 1768, we need not say much. Some of what he wrote

has been embodied in the foregoing chapters. His theory of acclimatization is peculiar. He thought it due to ' change of blood ' resulting from ' change of diet ' in a new country. The state was consequently hastened by repeated small bleedings so that the old blood might be replaced by the new, supplied by the food and water of the new country, whereby it would become composed of the same materials as that of the natives and the newcomers would more readily acquire the natives' immunity to disease. If, however, the bleedings were too great, the resulting weakness increased the liability to fever.

Lind notes the unhealthiness of the West Coast of Africa, in Senegal where a ' low malignant fever ' spreads among the Europeans soon after the start of the rainy season and where " fluxes, dropsies, jaundice and ague-cakes " are common, but " the greatest plague was the mosquetoes and sandflies, whose incessant buzz and painful stings were more insupportable than any symptom of the fever." He did not connect the two any more than he did the proximity to marshes and mosquitoes with malaria, though, as we saw in the introductory chapters, he came very near to it. He has little but ill to say of Batavia " where the Dutch have adorned the place with intersecting canals to make it resemble their European cities."

Replete with water these canals may perhaps serve for some use, or rather for ornament, but in the hot and unwholesome climate of Java, during and after the rainy season, they become extremely noxious to the inhabitants ; but more particularly to strangers. The unwholesome air of that place has cut off more Europeans than have fallen by the sword in all the bloody wars carried on by the Dutch in that part of the world.

Crews on ships suffered much, but not more than those on shore where " streets were crowded with funerals, bells tolling from morning to night, and horses jaded with dragging the dead in hearses to their graves."

He noted ' fluxes,' for which ipecacuanha was given, and in some the presence of liver abscess. The men of his day, the days before anæsthetics and in pre-antiseptic days, must have had wonderful pluck. Lind records the case of a seaman, thirty-five years of age, with signs of a large tumour in the left side ; suppuration was assisted by poultices and a month after the first onset of the pain the surgeon laid the tumour open for about six inches and let out nearly three pints of pus. He introduced his hand and found the left lobe [of the liver] containing honeycombed cavities. Discharge continued, but a sinus appeared towards the

umbilicus and another towards the back ; he laid them both open and filled the cavities with soft lint. After fomenting, he says, " I threw into the cavity an injection of barley-water and tincture of myrrh, which I repeated three or four times until I thought the parts were sufficiently cleaned of matter." The surgeon, Mr. Bogue, states that the patient " was dispirited on the thoughts of its [the tumour in the side] being opened." The patient returned to duty and within a fortnight was killed in action.

Lind, as others before and after his day, confuses yellow fever with other fevers. The idea of the infection having been brought to the West Indies by a ship from Siam (see Yellow Fever) is, he says, " truly chimerical, as similar diseases have made their appearance, *not only in the East Indies* [italics not in original] but in some of the Southern parts of Europe . . . when the air was intensely hot and unwholesome."

He mentions as signs of an unhealthy country—not as causative of disease—sudden alteration of air from hot to cold at sunset, fogs, and " swarms of flies, gnats, and other insects which attend putrid air and unhealthy places covered with wood."

Employment especially unhealthy and often fatal for Europeans was cutting down woods, clearing the ground or travelling along rivers or swamps after sunset and " fetching meat, etc., after sunset from shore has destroyed every year several thousand seamen."

We have noted elsewhere Lind's remarks that ships facing away from the shore, or having the ports on the shore-side covered, or having a fire so that there was abundant smoke, did not suffer so severely from fever as did others which took no such precautionary measures ; also his recommendation of hospital ships or ' floating factories ' at a distance from the shore as preventing disease by removal from sources of infection.

PATRICK MANSON
(1844–1922)

Patrick Manson was born on 3rd October, 1844, at Cromlet Hill, Oldmeldrum, Aberdeenshire. There were nine in the family of which he was the second son. A story is told of his early helminthic bent when he shot a cat on his father's farm and was found examining a tapeworm in its interior.

Medicine was not his first love ; his intention in early life was to become an engineer and his aptness at mechanics led to his being apprenticed at the age of fifteen years to Messrs. Blaikie Brothers, ironmasters. His physique was not capable of the work entailed and he had to give it up. In 1860 he entered Aberdeen University, studying during the summer at Edinburgh also, and he passed his final examination before he was twenty —too young to take his degree. Between this and 1865 he visited the hospitals, medical schools and museums of London. In that year he took his M.B. degree and in the following the M.D. He forthwith set out for the Far East, being appointed in 1866 Medical Officer to the Chinese Imperial Maritime Customs at Formosa. In addition to his official duties he attended regularly at a native missionary hospital and practised among the local European and Chinese residents. After five years, in 1871, he left Formosa for Amoy where he spent most of the next twelve years. Here his duties were similar to those at his former station but he was also Medical Officer in charge of a hospital for European seamen, and of a Missionary Society's Hospital and of a dispensary for the Chinese. To his chagrin his attempts to carry out post-mortem examinations met with the strongest opposition from the people. He made good use of the clinical material at the hospitals for teaching students, intending to give them a good grounding before they left to settle in the neighbouring province.

Early in his career at Amoy he successfully removed some large elephantoid tumours and thus won the confidence and goodwill of the Chinese. The growth of his work will be understood when we hear that in 1871 his patients numbered 1930, but three years afterwards they had risen to 4476. In 1874 Manson returned

SIR PATRICK MANSON.
1844—1922.

(Photograph kindly lent by Dr. P H Manson

home but was back again in Amoy the following year. While at home he heard of Timothy Lewis's discovery in 1870–2 of the embryo of Filaria in the urine and blood of man. Lewis was not the first ; it had been found in Havana in 1863 by a French surgeon, Demarquay, in a case of chylous hydrocele, but not in the blood. In 1877 Lewis succeeded in finding the adult worm in the nævoid scrotum of a patient in whose blood the embryos were present. The preceding year Bancroft had found them in a lymphatic abscess and sent the specimens to Cobbold who named the worm *Filaria bancrofti*. On the 20th April, 1877, Bancroft, writing to Cobbold, said : "I have wondered if mosquitoes could suck up hæmatozoa and convey them to water. I will examine some mosquitoes that have bitten a patient, to see if they suck up the filariæ" [embryos].

Manson saw that there were several hiatuses in the account of this worm which needed to be filled ; the life-history was incomplete, its pathology and pathogeny very indefinite. If, as appeared more than likely, Filaria caused elephantoid disease, why are the embryos sometimes absent from the blood ; *vice versa*, why are the embryos found, not sometimes only, but often, without the presence of elephantoid disease ? Arguing from the clinical aspect Manson concluded that the lymph scrotum was due to glandular and lymphatic obstruction. On examining a number of Chinese at all ages, he found among 190 apparently quite healthy fifteen who had embryos in their blood ; further analysis showed that the incidence increased with advance in age from one in 17·5 in youth to one in three in old age. He argued that elephantiasis is a 'frequent accident' rather than a necessary consequence of filariasis, just as aneurysm may complicate or follow atheroma. By examining his subjects at frequent intervals Manson found that embryos might often be present in the night blood though search for them in the day had failed and he established the Law of Periodicity and its inversion if the habits of the patient were changed. His conclusions were scoffed at and the inquiry was often thrust at him as to "whether the Filariæ carried watches ?" He found further that this daily periodicity was not peculiar to *F. bancrofti*, but occurred also in *F. immitis* of the dog. Manson wrote : "It is marvellous how nature has adapted the habits of the filariæ to those of the mosquito." [1]

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[1] Most text-books note that the periodicity of appearance of the embryos is in order that they may be engulfed by the mosquitoes. The author unfortunately, though a great admirer of Manson and well aware that it is regarded as little short of rank heresy to disagree with anything that

Manson argued that all the embryos seen in the blood could not develop in the host without destroying themselves by killing the host and they must therefore find their way to other hosts, or some other host, for development, and since the embryos swarmed in the peripheral blood, some blood-sucking insect was the probable [necessary ?] intermediary—flea, bug, louse, mosquito, sandfly, etc. If, he continued, either of the first three were the intermediary, being cosmopolitan it would have by this time spread filariasis all over the globe.

By a happy, though not a properly reasoned, jump he nevertheless arrived at a correct conclusion. Thinking mosquitoes were warm-climate insects and knowing filariasis to be a warm-climate disease, he plumped for mosquitoes as the vectors. He proceeded to test his theory and in 1877–8 allowed mosquitoes to feed upon a man whose blood was swarming with the embryos. Subsequent examination showed him that many of them died in the stomach of the insect, but some at least continued to develop. In those mosquitoes which had lived long enough he found the developing stages. Manson made in the case of Filaria the same statement, afterwards proved erroneous, that he subsequently made for malaria, that the mosquitoes die after ovipositing and by dying set free the developing embryos which thus infect the person who drinks the water.

Lewis in India in 1878 also noticed that the embryos underwent developmental changes in the thoracic and abdominal tissues of the mosquito and in 1881 W. W. Myers observed that filariasis did not spread in Formosa although the disease abounded on the mainland 180 miles away and he suggested that perhaps the proper mosquito did not occur on the island.

Manson expressed as an *obiter dictum*, cannot assent to this ; there seems to be no grounds, no justification for ascribing to a Filaria a mentality so advanced. The statement as so often made and as expressed by Manson that " filarial periodicity is an adaptation of the habits of the filaria to those of the mosquito, the intermediary host indispensable to the future life of the parasite " is surely an example of ὕστερον πρότερον. The Culex is the intermediate host because it appears at night and bites man when the embryos are in the peripheral blood stream, and not *vice versa*. Pure coincidence in the first place would explain things equally well. The Filaria periodically discharges the embryos ; doubtless most are destroyed but some reach the surface at a time when a mosquito of nocturnal habits is about and get taken up. If the Culex was a midday frequenter only, another insect would take on the part ; it is not likely that the Filaria would reconsider matters and change its habits. Moreover, change of habits by the patient changes the time of oviposition and either the day-embryo patients are less likely to transmit infection (if the Culex or a nocturnal mosquito is the only vector) or some other, a day-biting mosquito, takes on the duty.

Repeating his work in 1883 and following it up Manson found that of four species of mosquitoes prevalent in Amoy in two only, namely Stegomyia (now Aëdes) and Culex did development of the filaria embryo take place and in the latter only of these, *Culex fatigans*, did it come to completion.

An anonymous reviewer in the *Veterinarian*, March 1883, suggested that the larva when fully developed in the mosquito might be deposited in the act of biting and feeding, but it was not till sixteen years later that the younger Bancroft in Australia in 1889 (and G. C. Low in England in 1900 with infected mosquitoes sent to Manson by Bancroft) showed that this hypothesis was the true one. S. P. James, in India, in the same year (1900) demonstrated that *Anopheles rossi* was an efficient intermediary in that country.

It may be said that this discovery of Manson—that the mosquito was an intermediary host in which development took place (as opposed to mere mechanical transference)—paved the way to the subsequent discoveries of Ross at Manson's instigation of malaria being similarly transmitted. Nay, more, Manson's helminthic bent was shown in the latter also, for there is little doubt that he regarded the " travelling vermicule," or the stage succeeding that of zygote, as a small worm.

The idea of blood-sucking insects being transmitters of disease was not new in Manson's day. Native and untutored races spoke of *surra*, a disease of equines and camels, as being transmitted by gad-flies ; the natives of Africa connected *nagana* with ' fly ' ; Beauperthuy and, later, Finlay had suggested the theory of the ' tiger mosquito ' conveying yellow fever. Manson, however, has the priority of discovering that a particular blood-sucking insect is a necessary intermediary in the propagation of a specific disease —a discovery of the utmost importance to medicine, not only human but veterinary also, and particularly to tropical medicine.

We cannot dwell longer on Manson's work in helminthology, except to say a few words on one, possibly two, of importance. Passing mention may be made of his studies on *Filaria immitis* and *Filaria sanguinolenta* in the blood of dogs, on *F. corvi-torquati* in the white-necked crow, *E. picæ mediæ* in the Amoy magpie, *F. papillosa* in the eye of the horse, *F. (Oxyspirura) mansoni* in fowls. His share, however, in the discovery of Paragonimus, the lung-fluke, merits a longer reference. Ringer, in 1878, when carrying out a post-mortem examination on a Portuguese in Formosa who had been under Manson's care in Amoy for thoracic aneurysm, found certain parasites in the lungs, and reported the

fact to Manson. Nine months or so later a Chinese called to consult Manson for a skin eruption and, to Manson's disgust the patient after clearing his throat spat on the consulting-room floor. Noticing that the deposit was bloodstained Manson examined it under his microscope and found in it an operculated egg. He communicated with Ringer who in return sent the parasitic fluke found in the Portuguese, and which he had preserved. Examining the sediment Manson discovered more ova resembling that which he had seen in the sputum of his Chinese patient. This ovum was that of the fluke which came to be called *Distoma ringeri* (now *Paragonimus westermanii*), the latter specific name having previously been given to this fluke in the tiger.

One other discovery worthy of note was that of small platyhelminths found by Manson when he was performing an autopsy surreptitiously at night by lantern light in a Chinese cemetery, searching for adult Filariæ. He did not succeed in his quest for the latter, but the former—called at first, by Cobbold, *Ligula mansoni*—proved to be the plerocercoid stage, or Sparganum, of a Diphyllobothrium. The adult is, therefore, *Diphyllobothrium mansoni*, a parasite in nature of the dog and cat, the Sparganum stage occurring in frogs and snakes. Man becomes infested by using a split frog as a foment application to wounds—a common mode of treatment in China.

In 1879 Manson noted the organism which had been discovered by Hansen in 1874. He observed it in leproma juice but warned medical men against too ready acceptance of its being causative because " the present is the age of bacteria and as they are searched for everywhere and in nearly every disease, they are found everywhere and in every disease." This recalls once again the dictum of Pasteur.

In December 1883, Manson moved from Amoy to Hong Kong where at first his practice was mostly among the poorer Europeans and Eurasians. He took a leading part in establishing a dairy farm for supplying purer milk to children and the sick. This has since developed to a large and flourishing business concern, partly under Government supervision. Manson also took supreme interest in the then new Alice Memorial Hospital and made use of the clinical material there for teaching, making it in fact a school of medicine—the precursor of the present Victoria University and Medical School of Hong Kong. In 1886 he became Chairman of the Hospital Committee and the following year was elected

Dean of the proposed College of Medicine. In 1886 his *alma mater*, Aberdeen, gave him his first honorary degree, the LL.D. In 1889 he left Hong Kong and in 1890 settled in Queen Anne Street, London. Less than two years later, in May 1892, he was unanimously elected Physician to the Seamen's Hospital Society. Now came his first acquaintance with trypanosomiasis, sleeping sickness or, as it was then designated, Negro lethargy, through correspondence with the ill-fated Roger Casement, then in the Consular Service and stationed at that time in Sierra Leone.

In 1894 Manson started to give his public lectures on Tropical Medicine, first to missionaries proceeding to the tropics from Livingstone College, Leytonstone ; later the same year he was appointed to lecture at Charing Cross and St. George's Hospitals and in 1897 became Medical Adviser to the Secretary of State for the Colonies. Apart from the enormous gain in prestige conferred by such an appointment he thus met men going to and returning from all parts of the Empire and had his interest roused in matters which till then were known to him by little more than their names. Medical officers were encouraged to furnish reports regularly each year and to contribute in them, and to medical literature with a wider public, papers on subjects of interest. In 1898 his activities were added to by his being appointed lecturer at the Royal Free Hospital for Women, a post which he held for fourteen years. In the same year appeared his *Manual of Tropical Diseases*, a work which has passed through several editions and, much enlarged, is brought up to date from time to time under the able editorship of his son-in-law, Dr. Philip Henry Manson-Bahr, now Senior Physician to the Tropical Diseases Hospital, London, and Consulting Physician to the Colonial Office. For the first time a section of Tropical Medicine was organized at the meeting of the British Medical Association at Edinburgh, through his instrumentality, and he demonstrated some of Ross's work on the life-history of the parasite of malaria. The year 1900 witnessed his being awarded the Companionship of the Most Distinguished Order of St. Michael and St. George (Knighthood of the same Order followed three years later and the G.C.M.G. in 1912), and his election as a Fellow of the Royal Society of London. Other honours which may be mentioned here were the honorary degrees of Doctor of Science of Oxford University conferred on him in 1904, the LL.D. of Hong Kong University in 1919, and the LL.D. of Cambridge in 1921. In 1907 the Society (now a Royal Society) of Tropical Medicine and Hygiene was formed, with Manson as its first President.

His work, through Ross whom he aided, supported, encouraged and, in part, directed, in bringing to a successful issue the history of the life of the malaria parasite has already been dealt with at length (see Malaria).

Manson's other contributions to science—for, though settled in London, he contrived to keep his knowledge of tropical medicine not merely abreast of but, if we may say so, even ahead of the time—can be mentioned but briefly ; they are mostly returns to his first love, Helminthology. These were in connection with *Filaria diurna*, now *Loa loa*, and its life-history—the conjecture of a fly, Chrysops, as the intermediate host receiving proof by Professor R. T. Leiper more than twenty years afterwards. Next, *Filaria perstans*, so far as we know a harmless infestor of man, whose embryos he found in the blood of sleeping-sickness patients, and which he thought might be the cause of the disease—a pardonable error, because without full experimental proof he would never advance more than a conjecture. Again, though this is not in chronological order, for it occurred in 1894, he confirmed the development of guinea-worm (*Dracunculus medinensis*) in the Cyclops, which had been observed by Fedchenko twenty-five years before. His interest in avitaminosis—though that designation was not known at the time—is shown in his correspondence with Dr. Stanton (later Sir Thomas Stanton, a successor of Manson as Chief Medical Adviser to the Secretary of State for the Colonies) relative to the researches of the latter into the ætiology of beriberi.

There remains to be chronicled what may justly be regarded as Manson's greatest work in furthering knowledge of Tropical Medicine and Hygiene, namely the founding of the London School of Tropical Medicine. It seems astonishing to us now, on looking back, to find that a country with colonies and settlements in the tropics for nearly 300 years had no institution for systematic teaching of tropical medicine and hygiene, beyond the lectures at the hospitals referred to above—Charing Cross, St. George's and the Royal Free, at each of which Manson was the lecturer —and this despite the fact that 20 per cent. of the medical graduates of Great Britain were practising in warm climates.

In 1897 he met the Secretary of the Seamen's Hospital Society in the Resident's room at the Albert Dock Hospital and put before him a scheme for utilizing the hospital facilities for teaching. So rapidly did matters progress that in less than six months he was able to put forward a completed scheme. Joseph Chamberlain, the Colonial Secretary of the time, was quick to see what this would mean. He was a man interested throughout his public life

in questions of the health of the people. It is said that he chose the post of Colonial Secretary because he saw that disease and insanitation among the natives was paralysing their working capacity and proving inimical to administration and trade. In 1898 he addressed a letter to the General Medical Council and to the leading Medical Schools pointing out the importance of ensuring that medical officers proceeding to the tropics should have expert knowledge and stating his intention of giving preference, when filling up medical appointments in the Colonies, to those who had studied this branch of medicine. The General Medical Council, while not recommending that tropical medicine should be an obligatory subject for the medical curriculum, thought it advisable that Government should arrange for special instruction in tropical medicine, hygiene and climatology for qualified practitioners selected for the Colonial Medical Service.

In Chamberlain, Manson found one who fully appreciated his point of view and the statesman's driving force soon brought fulfilment. In this way, as well as by his own investigations, we may agree with Raphael Blanchard in his designation of Manson as " the Father of the Science of Tropical Medicine." Wasting no time, Chamberlain wrote to the Board of Management of the Seamen's Hospital Society asking them to establish a school for instruction in tropical diseases. A subcommittee was appointed which included Mr. H. J. Read (later Sir Herbert Read, Governor of Mauritius) of the Colonial Office, and in March 1899 made its report, recommending :

1. That the name of the School be the London School of Tropical Medicine in connection with the Seamen's Hospital Society.

2. That the first teachers in the School and the additional members of the Honorary Medical Staff be appointed by the Committee of Management of the Seamen's Hospital Society in consultation with the Advisory Committee.

3. That an advertisement be inserted in *The Times* and the medical papers inviting application for appointments on the Teaching Staff and the Honorary Medical Staff of the Hospital.

4. That there should be three sessions of three months each yearly.

On 3rd October, 1899, the first session was started with twenty-seven students.

After a few years the money raised proved inadequate for carrying out all that was desired and in 1912 Mr. (later Sir) Austen Chamberlain made an appeal in memory of his father, who died in July, 1914, and a sum of £73,000 was obtained which was allocated to the upkeep of the hospital, provision of new apparatus and of means for research. In 1920 a special Milner Fund of £100,000

was raised and the school was transferred from the Albert Dock to Endsleigh Gardens, London, now the Tropical Diseases Hospital.

A little more than two years later, by which time over 2500 students had taken the courses of instruction, Patrick Manson reached the end of a life crowded with work which has benefited mankind.

Other tropical schools had sprung into being ; that at Liverpool preceded the London School by a few weeks ; Germany founded her *Institut für Schiffs- und Tropen-Krankheiten* at Hamburg in 1900, and Belgium established a State School the following year. Others were founded later, in Paris, Bordeaux, Marseilles, in Italy, India and the United States of America.

Though he knew of the proposed incorporation of the School of Tropical Medicine with the London School of Hygiene and took much interest in the plans, he did not live to see its fulfilment— a consummation which owes much to the wonderful gift of the Rockefeller Foundation, of 2,000,000 dollars.

Manson passed away on the 9th April, 1922, in his seventy-eighth year, having worked almost to the last, hobbling with the aid of a stick, or being wheeled from bed to bed in the hospital, benignant, kindly, sympathetic, patient with everything but slackness and insincerity, courteous to all. Could there be a sounder piece of advice to the research worker than this dictum of Manson's ?

Never refuse to see what you do not want to see, or what might go against your own cherished hypothesis, or against the views of authorities. These are just the clues to follow up, as is also, and emphatically so, the thing you have never seen or heard of before. The thing you cannot get a pigeon-hole for is the finger-point showing the way to discovery.

This and Pasteur's equally valid dictum : " Be very careful when you are looking for a thing, or you will be sure to find it," might profitably be written up in every laboratory as a guide for all who are engaged in research.

Dying, Manson left a memory enshrined and enthroned in the hearts of his many pupils. There is no death for such as this !

HIDEYO NOGUCHI
(1876-1928)

Hideyo Noguchi was born on 24th November, 1876, at Inawashiro, Yama, Fukushima, Japan. He suffered a severe injury to his left hand, arm and foot, and less to the right hand, as a child, which caused the loss of fingers of the left hand and permanent crippling; all pictures taken of him show him hiding this hand. At the age of seventeen he began to study medicine in the university of Tokyo and on graduation in 1897 he obtained a post at the Baron Sato Hospital. From 1898 to 1900 he was assistant to Kitasato at the Institute for Infectious Diseases, Tokyo, and at the same time lectured on bacteriology at the Dental Institute there.

He crossed to America in 1901 and for three years was assistant pathologist to Simon Flexner at the University of Pennsylvania and in 1903 was given charge of the research department of the Carnegie Institute, Washington. He next came over to Europe and in 1903–04 worked under Professor Madsen at the State Serum Institute, Copenhagen, Denmark. Thence he returned again to the United States and engaged in research at the recently founded laboratories of the Rockefeller Institute. On his return he was given the honorary degree of Master of Science at the University of Pennsylvania which, it appears, had been promised (or suggested) before he went to Copenhagen and while in Denmark he was awarded the Royal Medal. In December 1914 he was offered the Directorship of Research at Mount Sinai Hospital, with a salary of 6000 dollars a year. He discussed this offer with Flexner who persuaded him to remain at the Rockefeller Institute, promising him a permanent post there at a salary of 5000 dollars. He remained a member of the Institute staff till his death.

At an early stage of his career in research he studied the question of toxins and antitoxins, agglutinins, hæmolysins and venoms. In 1909 the Carnegie Institute published his monograph on Snake Venoms. Noguchi turned next to the study and cultivation of Spirochætes. He recognized and demonstrated the *Sp. pallida* in the cerebral cortex of patients dead of general paralysis and in

the cord of tabetics. He sent slides over to Madsen in Copenhagen saying that he had found the spirochæte in forty-eight cases of general paralysis and one of tabes dorsalis.

Trachoma next claimed his attention and he cultivated a bacillus which he regarded as causative in that it produced the condition when inoculated locally into the cornea of monkeys. He also isolated *Bartonella bacilliformis* from the blood of patients dead of Oroya fever and from the cutaneous lesions of *Verruga peruviana*, confirming the fundamental identity of these conditions previously thought to be distinct. Barton, a Peruvian doctor, had seen these intracorpuscular bodies in 1909 and thought they were bacteria. Harvard doctors were of opinion that they lay somewhere between bacteria and protozoa and the name ' Bartonia ' was at first given to them. This name had, however, been preempted by Cossmann for an eocene mollusc, *Bartonia cancaliculatum*, so the name *Bartonella bacilliformis* was adopted.

Other subjects of study by Noguchi were anterior poliomyelitis, rabies, hog-cholera, the virus of herpes and Rocky Mountain fever. He cultivated Rickettsia-like bodies from the transmitting tick of the last named and noted the similarity between this and the tsutsugamushi disease, or Japanese River fever. He attempted with Flexner to cultivate the causative ' organism ' of anterior poliomyelitis with a view to obtaining an antiserum.

In 1918 Noguchi went to South America as bacteriologist to the Rockefeller Commission for the study of yellow fever. He was not in the best of health and it had been found that he was suffering from diabetes. He went first to Guayaquil. Yellow fever was then thought to be a spirochætal disease allied to infective jaundice. In Guayaquil, in Peru, in Brazil at the Oswaldo Cruz Institute, and Mexico he cultivated an organism from supposed yellow-fever cases and even thought he had succeeded in transmitting it from guinea-pig to guinea-pig by the agency of the mosquito (see Yellow Fever) and prepared with it a vaccine and furnished reports indicating that protection had been conferred by its use. He it was who first introduced the name Leptospira for the peculiar spirochæte of Weil's disease—infective jaundice. Hence the name given to his ' new organism ' *Leptospira icteroides*. This discovery and the results that followed have been described fully enough in the chapter of yellow fever and will not be repeated here. We have already related how doubts began to arise as to its accredited ætiological rôle.

In February 1924 he visited Kingston, Jamaica, and read two

HIDEYO NOGUCHI.
1876—1928.

[From a photograph at the London School of Hygiene and Tropical Medicine

papers there : one on health problems in tropical America, the other on Yellow Fever in Brazil. His views on the Leptospira as the cause of the latter were not accepted, Agramonte of Cuba being entirely sceptical. This scepticism made him very depressed and unhappy, and still more so when workers in West Africa were unable to find the organism. Dr. White now suggested his going to the West Coast to see if the disease there was the same as that of Brazil, in other words to prove his thesis. After some delay he agreed to go, though not till the end of 1927. His friends were averse to his undertaking the expedition. He was not in the best of health ; though he made light of it he was well aware that he was diabetic and he was fifty-one years of age. All his scientific life he had been an indefatigable worker ; it was by no means an uncommon thing for him to stay working all night in his laboratory. His friend Araki used to call him a " twenty-four hour man " ; he took very little sleep, but when he slept he " slept like the dead."

He accordingly sailed for West Africa, arriving in November. At first he was undecided whether to carry out his investigations in Nigeria or in the Gold Coast, but finally decided on Accra because there was more yellow ˈfever there. He worked at the Research Institute from November 1927. On Christmas Eve he dined with the other doctors ; the next day he did not visit the laboratory—a most unusual thing with him—and the following day was taken to hospital. He soon recovered and continued his researches, but gradually the fact that yellow fever in Africa was not due to a Leptospira was borne in upon him and that either African yellow fever was not the same disease as that in South America or that there was some fundamental error in the South American work.

He was very sad and depressed ; as he himself said, " It is the sunset of Noguchi." Nevertheless he worked on till the beginning of May 1928. On Sunday, the 9th, he played chess—a favourite game with him—till 11 p.m. and then went to the laboratory where he stayed all night. He had planned to return to the United States, but wished to pay a visit to friends at Lagos before leaving Africa. He went there on the Thursday and seemed to be in fair health, but on Friday, the 12th, he had a chill. His blood was examined for malaria parasites but none was seen. He returned to Accra and on the following day Dr. A. J. R. O'Brien (now Chief Medical Adviser to the Secretary of State for the Colonies) had him removed to hospital. On the Monday (the 15th) his temperature dropped, the usual lull in the course of

yellow fever. He seemed to be gradually improving when on the morning of Saturday, the 20th, he had an epileptiform seizure. He died the next day, 21st, at noon. His wife, Mary Dartis, whom he had married on 10th April, 1911, survived him.

WALTER REED
(1851–1902)

Walter Reed was more fortunate than most scientists and epidemiologists since in his short life of fifty-one years he saw the tangible results of the application of his researches and had the satisfaction of observing their success in practice.

Walter Reed was born at Harrisonberg, Gloucester County, Virginia, on the 13th September, 1851 ; he was the fifth and youngest child of Lemuel Sutton Reed, a Methodist minister, and Pharaba White. In 1866 his family moved to Charlottesville and he attended in 1867 a course in Latin, Greek and English literature at the university of Virginia and the following year began the study of medicine. The authorities were at first averse to his starting at such an early age—he was only seventeen—but he succeeded in taking his M.D. degree after a year's work, the youngest graduate in medicine known. He went thence to Bellevue Medical College, New York, where he took a second degree in medicine after another year of study and obtained the posts of District Physician in New York, Brooklyn, and Assistant at the Children's Hospital, Randall's Island. His operative dexterity attracted the notice of J. C. Hutchinson, the surgeon, and through the recommendation of the latter Reed, though only twenty-two years old, was appointed one of the five Health Inspectors of the town.

In June 1874 he visited his father in Murfreesboro and there met Emilie Laurence, his future wife, the daughter of a North Carolina planter. Desirous of marrying and knowing that practice was an uphill struggle for an aspirant without influence at his back, he decided to become an Army Surgeon, as assuring him a certain future and a scientific career. He sat for the examination in February 1875 and in June was appointed Assistant Surgeon with the rank of First Lieutenant. He was stationed at first at Willet's Point, New York harbour, but shortly before his projected marriage in 1876 he was unexpectedly ordered to Arizona. In October of that year his fiancée set out from San Francisco

to join him, a difficult journey of twenty-two days overland at
that time.   After Arizona he was posted to other out of the way
stations, in Nebraska, Dakota, and the Southern and Eastern
States.   In 1880 he was promoted Captain and was for a time in
command at Fort McHenry, Baltimore, and took the opportunity
of studying physiology more deeply at Johns Hopkins University.
Again transferred to the West, he was in 1882 stationed in Western
Nebraska, living at Fort Omaha ;   in 1887 he was posted to Mount
Vernon Barracks, Alabama, a welcome change indeed from the
barren desolation and trying climate of Nebraska to the sunshine
and abundant vegetation of Alabama.

Feeling how difficult it was to keep in touch with the develop-
ments of science he, in 1889, asked to be allowed to pursue his
studies further, or to be given facilities to do so.   The Surgeon-
General so far met his wishes as to permit him to attend Johns
Hopkins University if he would study medicine and surgery, but
he was *not to do any laboratory work*.   In 1890 he was appointed
examiner of recruits at the Baltimore depot.   A new Surgeon
General having succeeded, the restriction regarding laboratory
work was rescinded and he took up the study of bacteriology and
pathology under Professor William Welch at the University.
Bacteriology was then a comparatively new science which interested
him deeply, and this interest was greatly stimulated by the then
recent discoveries of the causative organisms of tuberculosis,
cholera, leprosy, glanders, erysipelas, tetanus, pneumonia, typhoid
fever, malaria, amœbic dysentery, cerebrospinal fever and diph-
theria.   Among other questions he investigated the ' hog cholera '
bacillus, a research which stood him in good stead when the Com-
mission of which he was a member came to consider the claims of
Sanarelli's ' Bacillus icteroides ' to be the causative organism of
yellow fever.

From 1891 to 1893 he was in Dakota.   In 1892 he published
his first contribution to medical literature, the subject being the
Contagiousness of Erysipelas.

His next great opportunity came in 1893 when he was appointed
Curator of the Army Medical Museum and Professor of Bacteriology
and Clinical Microscopy at the Military Academy, Washington,
and given the rank of Major.   That year he wrote a paper, *Remarks
on the Cholera Spirillum* ;   in 1895 he published two papers on
Typhus and the following year one on the *Parasite of Malaria*.

When the Spanish-American War broke out in 1898 Reed
applied for active service and he was appointed on a Commission
to study Typhoid Fever which was rife among the troops in Cuba.

PLATE XII.

WALTER REED
1851—1902

[Photograph kindly lent by the London School of Hygiene and Tropical Medicine
[By permission of the Dean, Sir Wilson Jameson

The report of this Commission appeared in two volumes, showing the parts played by flies, by contact, and by polluted water.

In the meantime, on the 3rd July, 1897, the *British Medical Journal* published the discovery (?) of Sanarelli that yellow fever was due to an organism which he called *Bacillus icteroides*. Reed and his assistant, Dr. James Carroll, studied Sanarelli's claims and were able to show, and published their reasons and conclusions in the *Medical News* of the 22nd April, 1899, that ' Bacillus icteroides ' was the hog-cholera bacillus which had been the subject of intensive study by Reed at Baltimore eight years previously.

In the spring of 1900 a yellow-fever epidemic was raging in Havana among the American troops and it continued on through the summer. The United States authorities appointed a Yellow Fever Commission with Walter Reed as Director, James Carroll as Bacteriologist, Jesse Lazear as Entomologist, and Aristides Agramonte as Pathologist. Dr. H. R. Carter, working in Havana, had called attention to the fact that, although the incubation period of yellow fever was only up to five days, a house to which a patient was taken did not become infected—that is, other cases did not occur—until fifteen or more days had elapsed. Reed saw in part the significance of this, comparing it with the incubation period of malaria in the mosquito. He, therefore, instead of continuing his pursuit for a specific cause, turned his attention to studying the mode of conveyance of infection.

We need not dwell here on the heroic story of Carroll, Lazear and the volunteers at Camp Lazear. It has been told elsewhere in this work (see Yellow Fever) and it has been repeated till all the scientific world knows it by heart—of Dr. Carroll's allowing himself to be bitten by an infected mosquito, but not infective because sufficient time had not elapsed after the infective feed, and later the infection of the same investigator by an infective Aëdes (see also Life of James Carroll) with recovery, and of Lazear and his death on the 25th September, 1900. In the barracks at Pinar del Rio the disease was rife but was being diagnosed as " remitting or pernicious malarial fever " ; of thirty-seven patients eleven had died.

One particular instance put Reed on the track, or supported what till then was somewhat conjectural or not yet proven. On 6th June, 1901, a convict was brought to Pinar del Rio and placed with eight others. Just over five weeks later, on 12th July, he fell ill and died on the 18th, of yellow fever. He had all this time been under strict guard and therefore could not have contracted

the disease in the town of Pinar del Rio, nor from the other prisoners who all were and had been healthy. The inference was that he had been bitten by a stray infected insect which had entered by the cell window.

In October 1900 the Commission communicated to the Hygiene Congress at Indianapolis that mosquitoes were the intermediate host of yellow fever and on the 20th November there was erected, a mile distant from Quemados, ' Camp Lazear,' where further experiments in transmission to prove that Aëdes was the only vector in nature, that clothes, bedding, fomites, vomit and excreta were non-infective, were carried out, as has been related. Reed found that the disease could be produced by subcutaneous injection of blood from a patient in the first three days of illness.

At the Pan-American Congress held at Havana, 4th–7th February, 1901, the sequence of mosquito transmission was published in its fullness. In General M'Caw's *Walter Reed: a Memoir*, the author sums up in these words :

It has been well said that Reed's experiments will always remain as models in the annals of scientific research, both for the exactness with which they were adapted to the points to be proved, and the precautions taken that no experiment should be vitiated by failure to exclude all possible sources of error.

Later in the same month, February 1901, Reed returned to the work of his Professorship at Washington, charging Carroll to elucidate such secondary questions as the parts played by blood and the urine in yellow fever. In April Reed read a paper before the Medical Faculty of Maryland on the *Propagation of Yellow Fever*, illustrating the results of the Commission's researches. Gorgas, meanwhile, was carrying out preventive measures in Havana based on the findings in the report of the Commission and in less than a year Havana was free of the scourge.

In 1902 was issued the Report of the *Origin and Spread of Typhoid Fever in the United States Military Camps during the Spanish-American War*. This was a large work in two volumes ; the first dealt with the disease as it affected the various divisions, the second contained the maps, and the whole was a monumental work on the epidemiology of typhoid fever.

The same year Harvard University conferred on Reed the honorary degree of Master of Arts and Michigan the LL.D. The work of the last few years had made heavy demands on his vigour which was not restored by furlough. He spent the summers of 1901 and 1902 at his cottage near Monterry, Pennsylvania, but the signs of fatigue and strain persisted. During October he would return

from his day's work exhausted. In November, the 12th, he complained of abdominal pain and suspected appendicitis, a diagnosis confirmed on the 14th by his friend, W. C. Borden, a surgeon, who, however, advised postponing operation. The next day Reed felt much better, in fact he thought the danger was over for the time, but on the evening of the 16th the temperature rose and the pain returned. Borden then advocated operation which was performed at 11 a.m. the following day. The appendix was found enlarged, partly distended with pus, adherent to the colon and already ruptured. The viscus showed signs of previous attacks which probably explained the 'indigestion and colic' which had caused him trouble and discomfort for some years. The patient reacted badly to the operation, or the anæsthetic, and for the succeeding eighteen hours was constantly vomiting. He became depressed and restless. On the fifth day peritonitis set in and on the next day, 22nd November, 1902, he died.

He was buried three days later ; the service with full military honours took place in St. Thomas's Church, Washington. His remains rest in Arlington where eighteen years later W. C. Gorgas was laid to rest. A stone of black granite marks his grave ; it is inscribed : " He gave to man control over that dreadful scourge, Yellow Fever," a quotation from President Eliot's address when he conferred on Reed the M.A. of Harvard. A marble bust by Hans Schuler was erected in the Surgeon-General's Library at Washington.

A fund was collected, the proceeds of which were to be applied to the use of his widow and daughter during their lifetime, and after their deaths to the cost of a monument or the expenses of research in commemoration of Walter Reed.

> In Arlington his quiet ashes rest,
> Who was so restless in his earthly day ;
> Who put so well old theories to test
> That new ones were evolved ; who found a way
> To stay the ravage of an ancient scourge
> That had attacked from every swampish fen
> For ages, with a demoniac urge
> Working grim havoc with the race of men.
>
> A great hospital is his monument.
> How fitting that it is no needless thing
> To perish as the wheeling years are spent,
> Like others that have passed on silent wing
> But something to perpetuate his hand
> Among the broken bodies of the land.
>
> *Clarence Edwin Flynn.*

RONALD ROSS
(1857–1932)

The life of Ronald Ross enters so largely into the history of malaria that a detailed biography would entail a repetition of much that has been already given in the chapters dealing with that disease. In this place, therefore, we shall rest content with presenting a few of the facts of his life more of general than of special interest.

Ronald Ross was born at Almora in the Kumaon Hills, Northwest Nepal, on the 13th May, 1857, three days after the outbreak of the Indian Mutiny ; his family had been Anglo-Indians for three generations. His grandfather, Hugh Ross, a Lieutenant-Colonel in the Indian Army, died at Cawnpore in 1838 ; his father, Campbell Claye Ross, the second of six children, was born in 1823, joined the Gurkhas—68th Bengal Native Infantry—as ensign at the age of eighteen years and in 1856, at the age of thirty-three, he married Matilda Charlotte Elderton, the daughter of a London lawyer. At his death, which occurred in 1892, he was General Sir C. C. Ross, K.C.B.

Ronald Ross was the eldest of ten children. In his eighteenth year, on 1st October, 1874, he entered on the study of medicine at St. Bartholomew's Hospital Medical School. Medicine was not his only interest ; he was also a mathematician and a poet. He obtained the M.R.C.S. diploma in 1879 and for a time travelled between London and New York as a ship's surgeon. In 1881, as was customary in those days, he took the diploma of Licentiate of the Society of Apothecaries.

After a four-months' course at the Army Medical School, Netley, he entered the Madras Medical Service as Surgeon. He saw service in the Burma War and in the Andamans, at Port Blair, south-west of Rangoon. His first home leave in 1888 he spent in London, studying bacteriology under Klein, and took the D.P.H. The following year he married Rosa Bloxham, and on the 1st August left again for India.

In 1892 he began to take special interest in malaria, though

PLATE XIII.

SIR RONALD ROSS.
1857—1932.

[Photograph kindly lent by the Director Ross Institute

he had taken up the study of mosquitoes during his first tour of service. Much of the details of his scientific life subsequent to this has been given in the malaria sections of this work and need not be repeated. Here we speak of it on more general lines.

Although Laveran had discovered the parasites of malaria in 1880, Ross did not see, at least did not recognize, them until 1894 when they were demonstrated to him by Manson to whom Ross had been directed by Kanthack. At Manson's instigation Ross, in 1895, returned to India from his second home leave, ambitious to elucidate the ætiology of the disease. He arrived at Bombay on 21st April and was posted to Secunderabad. The temperature here was high, between 90° and 100° F. and he had no little difficulty in keeping specimens of blood and mosquitoes from drying before he could mount the former and dissect the latter for examination. These were the days when blood was examined in the fresh state for parasites.

After many trials he succeeded in showing that in dapple-winged mosquitoes—Anopheles—crescents underwent exflagellation in the mid-gut. Valuable time was lost, at least spent, in attempts to determine direct water-borne infection of man by infected mosquitoes.

In September 1895 he had to go to Bangalore on special sanitary duty, his investigations being on that account held up perforce for eighteen months. On the 27th May, 1896, he wrote home to Manson suggesting the possible conveyance of infection by the bite of the mosquito. Prosecuting again his dissection of mosquitoes he found that the flagella soon disappeared from, at least were no longer recognizable as such in, the stomach of the insect. On his return to Secunderabad, on 18th June, 1897, Ross proceeded to breed mosquitoes in the laboratory; he then allowed them to feed on a malarious patient and at intervals afterwards examined them. On 20th August, 1897—'Mosquito Day'—he saw pigmented cysts (oöcysts) in the wall of the stomach which had bitten the patient four days previously. These cysts measured 12–16 microns in diameter. If he waited for a longer time than four days the development had advanced to a larger stage. Two days later, in a letter to his wife, he enclosed the following triumphant pæan, which has become classical:

> This day relenting God
> Hath placed within my hand
> A wondrous thing; and God
> Be praised. At His command,

> Seeking His secret deeds
> With tears and toiling breath
> I find thy cunning seeds,
> O million murdering Death.
>
> I know this little thing
> A myriad men will save.
> O Death, where is thy sting ?
> Thy victory, O Grave ?

20th August—Mosquito Day—was celebrated in his honour for some years ; later the day of the annual celebration was changed to 13th May, Ross's birthday, for a joint commemoration to Manson and Ross.

Five weeks later, on 26th September, Ross to his chagrin was ordered to Kherwara in Rajputana where, owing to absence of malaria, he was unable to pursue his investigations. At Manson's intercession the Secretary of State for India granted Ross time for research and by 17th February, 1898, he was back in Calcutta.

In the meantime Manson had informed him of MacCallum's work, first in birds then in man (see Malaria), on the function of the microgametes (flagella) in impregnating the macrogametes.

Owing to the scarcity of human malaria at the time in Calcutta Ross studied the disease in birds and traced the development from oöcyst to sporocyst (these terms are modern ; those used by Ross are given in the chapters on Malaria) and the migration of sporozoites and he carried out numerous infection experiments with success. Ross's report to the Director-General of the Indian Medical Service is dated 21st May, 1898, and at the British Medical Association Meeting held at Edinburgh on the 24th July, Manson announced these results to the profession at large.

In September the same year Ross was sent to Assam to investigate and report on kala azar there. On the 22nd February, 1899, he left Calcutta and arrived in London on 20th March. The following month he was appointed Lecturer in Tropical Medicine at the Liverpool School and three months later retired from the Indian Medical Service with the rank of Major. The same year he went with H. E. Annett and E. E. Austen on an expedition to Sierra Leone, and in 1901 with Logan Taylor to the Gambia, Lagos and the Gold Coast. In June of the same year he was elected a Fellow of the Royal Society of London.

In 1902 he received the appointment of Professor of Tropical Medicine in the University of Liverpool and held this post for twelve years. In 1902 also he paid a visit to Suez and Ismailia, as has been recorded already (see Malaria). In 1904–05 he was

co-examiner with Patrick Manson and G. H. F. Nuttall for the Cambridge Diploma in Tropical Medicine and Hygiene, the first diploma in this subject to be established.

During his tenure of the Liverpool professorship he visited Mauritius in 1907–08 to investigate health conditions there in general and malaria in particular and to advise on antimalaria measures. From 1909 to 1911 he was President of the (now Royal) Society of Tropical Medicine and Hygiene. In 1912 he visited Spain, Greece and Cyprus on a similar mission to that of Mauritius and the same year he left Liverpool for London and became Physician for Tropical Diseases at King's College Hospital and the following year (1913) was appointed Professor of Tropical Sanitation at Liverpool and for a time continued to hold this Chair, travelling to Liverpool to deliver his courses of lectures.

Meanwhile, in 1908, he was given a Commission as Major in the Territorial Army Medical Corps and five years later was promoted Lieutenant-Colonel. In December the following year, four months after the outbreak of the European War he was appointed Consulting Physician for Tropical Diseases at the Base Hospitals for Indian troops in England and in 1915 was investigating dysentery, a disease rife at that time in the Dardanelles. In 1917 he was sent to Salonika on a malaria survey ; the ship in which he travelled was torpedoed. In 1918 he was made a temporary Lieutenant-Colonel in the Royal Army Medical Corps and after demobilization he practised in London. In 1925 he became Consultant on Malaria to the Ministry of Pensions.

The controversy with Grassi which was pursued for some years, a controversy which added nothing to the prestige or dignity of either contestant, regarding priority of discoveries has been sufficiently touched upon in the earlier chapters of this work and the true state of the facts, so far as we can give them, has been set down. After Ross's pioneer work on bird malaria it was not a matter of great difficulty to apply it to man and develop it, but much credit is due to Italian malariologists for subsequent investigations as has been pointed out.

Ross was a man whose kindly intellect and geniality won the hearts of many, whereas his pugnacity, his impatience with and hatred of inanition and incompetence made many hostile to him. As we have said, medicine was not his only love, nor was it his first love. His earliest wish and intention was to be an artist and even after he qualified in medicine he gave more time to mathematics and to poetry than to what was ostensibly his life-work. He wrote and published books of verse and several romances and,

from the scientific view, his best work, his *Memoirs*, in 1923.   He was awarded a Royal Gold Medal of the Royal Society in 1909. He was the recipient of many honours ; some have been mentioned such as his election to the Fellowship of the Royal Society in 1901 ; two years later he was a Vice-President.   The same year (1901) saw his election to the Fellowship of the Royal College of Surgeons of England.   In 1902 he was created Companion of the Bath in June, and received the Nobel Prize in December.   Trinity College, Dublin, conferred on him the degree of Sc.D. in 1904 ; Aberdeen the LL.D. in 1906.   In 1911 he became a Knight Commander of the Bath ; in 1914 he was awarded the Bisset Hawkins Medal of the Royal College of Physicians of London, a medal given every three years to a British subject who has, during the preceding ten years, done work in promoting Public Health such as deserves special recognition.   Towards the termination of the War, in June 1918, he was created Knight Commander of the Order of Saint Michael and Saint George.   In addition to the above he received other awards from foreign countries and was made an honorary member of many societies at home and abroad.

On 25th July, 1926, the Ross Institute and Hospital for Tropical Diseases, founded in his honour, was opened at Putney by His Royal Highness the Prince of Wales, afterwards King Edward VIII. Ross was its Director-in-Chief.

He was a sick man for some years before his death and had his full share of trouble.   In 1927 he had a stroke, but this abated but a little his interest in scientific work.   His elder son was killed in the Mons retreat and he lost one of his daughters—he had two sons and two daughters—in 1925, and his wife died in 1931.   During the succeeding year he became seriously ill and progressively lost strength.   His death took place at the Ross Institute on the 16th September, 1932.

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APPENDIX

CHAPTER III

THE COLONIES, PROTECTORATES AND DOMINIONS

FOREAMI AND NATIVE WELFARE

When writing of West African colonies we mentioned incidentally (p. 78) the advantages which civilization has brought to the natives of British and French territory in the way of education, of building roads, of opening up the hinterland and aiding commerce. Later (pp. 91-96) we spoke of British Colonial Medical development, embracing schemes for the welfare of the native, ante-natal and post-natal clinics, establishment of health units, of training centres for nurses and midwives, and research into the causation and prevention of disease.

There is, however, another important movement directed to improving the health and living conditions of the native which took its origin in Belgium and started work in the Belgian Congo in October 1930, and has attained such a level of importance as to warrant more than a mere passing reference.

To make a beginning a society collected a fund sufficient to yield an income of nine million francs. Its affairs were controlled by a Council and a Committee in Belgium and a Bureau at Brussels. There was also a local Committee in the Congo presided over by the Governor-General. The society goes by the name *Foreami*, a word made up of the chief letters of *Fonds Reine Elizabeth pour l'Assistance Médicale aux Indigènes du Congo Belge*, and its programme envisages complete medical assistance to natives in rural areas in the Belgian Congo. Though working in close association with the Government Medical Service it nevertheless pursues a separate policy and maintains a separate staff. The society originated in the following way. The Government Service in rural areas is composed of: (1) Itinerant missions primarily directed against sleeping sickness; (2) Rural dispensaries and dispensaries controlled by religious bodies; (3) Maternity and child welfare establishments, largely staffed by religious bodies.

Although these measures had proved their worth, Dr. Dupuy, Director of the Bas-Congo Sector, and Dr. Prati, Director of the Sleeping Sickness Mission, conceived the idea that examination and registration of whole populations in various areas were necessary for a successful campaign against sleeping sickness and that such a programme should be extended to cover all diseases. This was obviously impracticable at one time over the whole country of thirteen million inhabitants,

widely scattered, and the suggestion was made that the method should be applied to a limited area at first and extended later. A campaign was to be inaugurated to combat the great devastating diseases, sleeping sickness, smallpox, yaws, syphilis, leprosy, tuberculosis, helminthiasis and ulcers, and to reduce maternal and infant mortality. Funds were provided by the Belgian Government and Colonial Ministry and a large contribution was made by Queen Elizabeth.

A preliminary survey of the terrain was made and arrangements were carried out by which it was possible for natives to receive treatment within 15 kilometres of their homes. The first region to be dealt with was the Bas-Congo, and in 1934 the Government regarded the position there as so much improved that it could be left. Foreami therefore moved to the Kwango area in 1935, the medical care of the Bas-Congo remaining in the hands of the ordinary Government Medical Service.

At the height of its activity the Foreami had the services of 26 doctors, 23 sanitary workers, 4 medical missionaries and 40 members of religious organizations, together with a trained native staff of nearly five hundred. Its activities include the registration of *all* persons in the area .concerned, the periodic examination of *all* persons, the treatment of *all* diseases, the improvement of sanitation, the development of social work and the collection of statistics. In the peak year, 1936, the total examinations numbered 1,156,741, and 4475 new cases of trypanosomiasis were diagnosed.

It may be interesting to give a brief statement of the method of working. Each travelling unit consists of one doctor, one sanitary worker, three native microscopists, and a number of native dressers. These units supervise about 30,000 people, who are visited twice each year. About 400 persons may be examined in a day; the examination can, therefore, be superficial only. It is considered enough, however, for an expert to detect the principal diseases. The healthy are 'soon dismissed; suspects are given more attention, and these form in most places about one-fourth of the population.

CHAPTER V

MALARIA

Marshes and Fever

The close association between marshes and fever was noted by Varro in 36 B.C., as we have stated (p. 141), but the idea was far from being a new one then. Empedocles (504-443 B.C.) is reported to have carried out a hygienic achievement which, if rational at all, must have been based on knowledge of this association. In 480 B.C., or twenty years before the reputed date of the birth of Hippocrates, fever (probably malaria) was devastating the Sicilian town of Selinos. The district was of a swampy nature and was fed by two streams. Empedocles, by

joining the two streams, succeeded in draining the marsh and the pestilence was checked. It may, of course, have been merely the happy consequence of a general drainage measure, but was more probably the result of definite forethought because coins were struck in his honour to commemorate the benefits and the cessation of the outbreak. Examples of these coins are to be seen in the British Museum.

NOMENCLATURE OF THE MALARIA PARASITES

When speaking of *Plasmodium falciparum* as the name now generally applied to the parasite of subtertian malaria we pointed out grounds for its unsuitability (p. 155). Even now, however, among zoologists a certain degree of confusion exists regarding its correct name. The name is more widely adopted now than it was a few years ago, but some still persist in calling it *P. præcox*, and others *P. immaculatum*. *Plasmodium.præcox* Grassi and Feletti, 1890, is *de jure* the correct nomenclature, but Sergent and his co-workers support the recommendation of Christophers and Sinton that the strict application of the rules of nomenclature would lead to much confusion and that the three common specific names for the parasites of benign tertian, quartan and subtertian, *vivax*, *malariæ* and *falciparum* respectively, should be universally adopted. They further consider it desirable that the specific name *præcox* as the designation of the first avian plasmodium described by Grassi and Feletti should be abandoned. This should be called *Plasmodium relictum* Grassi and Feletti, 1891, and the name *præcox* for a plasmodium becomes therefore a *nomen nudum*.

DISTRIBUTION OF *Plasmodium ovale*

Of other forms of parasite records of late years show that infection by *P. ovale* (p. 155) is far from rare. In 1934 P. Mühlens reported a case in a patient in Western South America, and in September, 1939, Hernan Mendez placed on record infection of a child, four years of age, in Venezuela, the first report of a case from the northern section of South America. In the same year, a month earlier, Erich Bock published the results of a study he had made of twenty certain and one doubtful case of *P. ovale* infection. Of these, one came from Nigeria, one from Liberia, two from Spanish Guinea, one from Fernando Po, fifteen from the Cameroons, and one from East Africa. Of the places in the Cameroons from which these infections came Tiko stands first with eight. Bock considers that *P. ovale* is essentially an African species of parasite and is found particularly in Central Africa. He thinks that, as the morphology becomes better known, the positive findings outside Africa will increase. In a list (*Arch. f. Schiffs- u. Trop.-Hyg.* 1939, V. 43, pp. 327–52) he mentions thirty-five altogether in Africa, also the one of Mühlens mentioned above, and another in Russia, which, with that of Mendez, make three outside Africa.

The following year, 1940, de Meillon and Gear recorded the case of a woman who for the first time in her life visited a malarious country, to spend a fortnight in Southern Rhodesia. A week after her return she

became ill, and was found to have a *P. ovale* infection. This fact suffices to dispose of the view that this parasite is merely an abnormal form of *P. vivax* appearing in chronic infections. In the same year, 1940, cases were reported from Mauritius by Webb and Hervel. One was a Creole woman, an inmate of the Beau-Bassin Mental Hospital, another in the prison which is close to this hospital.

The average incubation period of infection by *P. ovale* was found to be ten days, with extremes of five and twenty-eight days. Bock, from his investigations, finds that *P. vivax* and *P. ovale* are immunologically different. During an infection he observed that the number of the nuclei of the dividing form varies. It may be that this feature is connected with the effect on the parasite of the metabolic activities of the body of the host, or is an expression of degeneration. From a consideration of the morphological, clinical and immunological features there is little doubt that *Plasmodium ovale* should be recognized as a definite malaria species.

NATURALISTIC MEASURES IN MALARIA CONTROL

Though different localities, with differences in rainfall, climate insect fauna, opportunities for re-introduction of infection, engineering projects and so forth, will afford each its problems in malaria control, there are certain general lines along which success has been attained, designated Naturalistic Measures, of which it is well to give a summary. The principles of these measures were set forth in a Bulletin of the Health Organization of the League of Nations, issued in December 1938. This report was the joint work of four well-known malariologists —L. W. Hackett, P. F. Russell, J. W. Scharff and R. Senior White.

" Naturalistic Control " is a term introduced by K. B. Williamson and, as regards the entomological factor in malaria, may be defined as " the deliberate extension or intensification of natural processes which tend to limit the production of mosquitoes or their contact with man," as opposed to restriction by artificial or conscious intervention as by ditching, screening, Paris green, insecticide sprays.

In nature we find that every species of Anopheles is restricted to certain types of surface water in which alone it can breed in effective numbers; also, of the 180 or more potential vectors—*i.e.* hosts in laboratory experiment—the great majority do not come into frequent and repeated contact with man. In the plain of Naples both these factors are found in the marshy area, Orti di Schito, in the delta of the river Sarno, near Pompeii. This is now a patchwork of small market gardens intersected by numerous canals. None of the dangerous vectors of Southern Europe—*A. atroparvus, elutus, labranchiæ, superpictus*— adapts itself to the fresh and flowing water; *A. typicus* and *bifurcatus* breed well, but they rarely feed on man. So here there is ' natural ' control and no special antimalarial measures are needed.

Zendrini invented automatic gates, which were erected in .1740 in the canal at Viareggio. They open in winter, or when the water in the canal is higher than the sea; close in the dry summer season when the level in the marshes is low and the sea would otherwise flow in. The character of the larval habitat round Viareggio completely changes,

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and there have thus been artificially produced the 'natural' barriers as seen at Orti di Schito.

Naturalistic methods may be classed as chemical, physical, or biological, and they may be directed against the larval, aquatic stages of the mosquitoes or against the adults. As the whole question is so important we must say a few words on the main principles of these methods.

I. Against the Larval Stages.

(a) CHEMICAL:

i. *Pollution of water*, as by turning industrial and organic wastes, sullage, and soapy water from houses into the breeding places of the mosquitoes. For example, passing bargasse from sugar-cane mills in the Philippines kept a stream free from *A. flavirostris*; and, in Ceylon, the refuse from a Government Sisal Experiment Station had the same effect. Green-cut vegetation, on the same principle as Herbage Packing, when thrown into borrow-pits inhibits Anophelines but not Culicines.

ii. *Changing the Salt Content of water.* An example of this has already been given—namely, that of Viareggio, where the brackish water lagoon was changed into fresh marsh water. In Durazzo, Albania, the opposite of this was effected and a marsh was led into a seawater lagoon and, by reversing the tide-gate, the salt water was allowed to enter, and this stopped the breeding of *A. elutus.*

(b) PHYSICAL.

i. *Natural filling and silting.* Examples of this are to be seen at Ravenna and Grosseto, where rivers from the Apennines bring waters with 16 per cent. suspended matter and in a single winter 30 cm. or more may be deposited over many thousand acres. In Assam, in 1932, a marsh was converted into sandy flats by diverting into it a silt-bearing stream.

ii. *Sluicing.* This is finding increasing application; its effectiveness depends on turbulence, splashing, stranding, and stirring up of silt.

iii. *Flooding.* The annual flooding of the Bengal delta is an instance of natural control. The silty flood waters, inimical to local vectors, and the general rise of the deposit reduced the amount of the 'breeding edge.'

iv. *Fluctuating water-level.* This tends to strand larvæ and hinder the growth of protective floatage, to kill aquatic vegetation in the shallows and to deprive the larvæ of their protection from natural enemies. In the Tiber delta a large marsh is surrounded by an embankment and is periodically filled from the river by pumping to irrigate a tract of land; the rapid changes in water level prevent aquatic vegetation maintaining itself. In Malaya, a saline pool had *A. sundaicus* breeding at the edge; it was opened to the tide, and the rise and fall got rid of the larvæ, though there was no change in the flora or fauna.

v. *Intermittent drying.* This is useful for dealing with rice-fields, as in Bulgaria, Egypt and Madras. In the Dutch East Indies intermittent draining reduced *A. aconitus* density by one-third in 1937, without any ill effect on the yield of rice; in fact, some planters reported an improved yield. ·

vi. *Agitation of the Water Surface.* Certain pools on farms on Penang Hill were fed by water from jungle-protected hill streams carried on split-bamboo conduits ending four feet above the pools. The splashing and rippling of the surface prevented mosquito breeding.

vii. *Stagnating* (ponding). In Malaya a hill stream was made into a series of pools by earth and timber dams; pond plants and larvivorous fish were introduced. *A. maculatus* ceased to breed.

viii. *Muddying* effected by silt and sluices, the 'flood flush.' This has been found good in the Bengal delta, but will not do for all species. For example, though the turbidity from ploughing the rice fields proved useful in Malaya, larvæ of *A. pharoensis* were found to be present in rice fields and ditches flooded by turbid Nile water.

ix. *Shading or clearing.* The natural habitat of *A. umbrosus* is peaty marsh in virgin jungle, whereas that of *A. maculatus* is the seepage areas in sunlight or hill streams open to the sky. Hill streams which are shaded by jungle breed only members of the *aitkeni* group, all of which are non-vectors. Clearing of streams by the villagers for cultivation of plantations led to the disappearance of *aitkeni* and the breeding of *A. maculatus* in Malaya and of *minimus* in Assam.

x. *Drying land by planting trees.* De Boer has reported good results from this measure in Uganda, but the same ends are attained more quickly and often more satisfactorily by simple drainage.

(c) BIOLOGICAL.

i. *Use of fish and other natural enemies.*

ii. *Changing the fauna and flora.* The cultivations of *Chanos chanos,* a fish used for food in Java, in the salt ponds in which *A. ludlowi* breed, and also of algæ used by the fish for food. Malaria is said to have been practically abolished in parts round Batavia by laying the ponds dry for two days every month and filling them again with fresh sea-water. The fish do not die because they remain in the side ditches. This method must not, however, be applied indiscriminately for, in India, for example, cleaning of the village tanks got rid of the *annularis* group, which are poor vectors, and removal of *Pistia stratiotes* let in the dangerous vector, *A. varuna,* which grew at the cleaned edge against the tree roots.

II. Against Adult Mosquitoes.

(a) CHEMICAL.—There are several theoretical suggestions to this end, but they have little or no scientific support.

  i. *Creating repellent barriers of odorous plants.*

  ii. The use of *drugs to cause odorous perspiration—e.g.* sulphur. The former of these has no support and, as regards the latter, no drug has been found to have such an effect.

(b) PHYSICAL.

  i. *Clearing*, and destruction thereby of shelters. This may be done over a small radius around dwellings, but often has no beneficial effect and, as often as not, does harm.

  ii. *Creation of plant barriers* to obstruct flight. This, again, is purely theoretical and there is no scientific evidence that it can be done.

  iii. *Rendering rooms unattractive as resting places* for mosquitoes. No means are known of effecting this.

(c) BIOLOGICAL.

  i. *Introduction of natural enemies.* This is not a measure which has proved of value for adult mosquitoes as it has for larvæ. Bats and spiders are believed to catch them, but of this there is no real proof.

  ii. *Winter killing.*—This also is fallacious. A cold winter or spring makes little or no difference to the anopheline density in the succeeding summer.

  iii. *Deviation by animals*, or Zoophily, is the only measure of proved value against adult mosquitoes. Of the 180 species of Anopheles, only twenty-four or so have been shown to include man in their normal range of preferred hosts, and only fifteen of these have been incriminated as vectors over more or less widespread areas; some are vectors only by force of the enormous numbers in which they are produced. If the other hosts sufficiently outnumber man the vectorial capacity of such species would disappear. "A mosquito must bite two different men to transmit malaria, so animal deviation acts to square, not double, the chances against transference of infection." Thus *A. maculatus*, the all-important carrier in the Malayan hills, has but little significance in the malarious areas of Assam and Southern India.

    Toumanoff, in 1936, in French Indo-China, showed that the chief carriers, *A. minimus* and *A. jeyporiensis*, var. *candidiensis*, behave differently under stabular attraction. The latter is more susceptible, whereas more than 50 per cent. of *minimus* cannot be thus diverted. Examining many other vectors, less important than the two mentioned above, he showed that they were almost completely deviated by animals but, in the absence of the latter, could be very dangerous to man.

    Falleroni at Ardea, Rome Province, in 1933 used this natur-

alistic control method with great success by constructing a ring of pigstyes round a small village; there followed marked diminution in malaria (the vector in this instance was *labranchiæ*, which has a strong bias for human blood). On the other hand, Barker and Rice in Greece found *A. elutus* was more attracted to local domestic animals than to man and turned readily from the latter to the former. *A. flavirostris* is another species which bites man or animals indiscriminately, and in this case animals do not afford an effective protection.

The above is perhaps an inadequate summary of a very important question, but it will indicate measures that are potentially adaptable to rural areas where carrying out of other methods of control has been found impossible. With increased knowledge of mosquito ecology further advances may be made with the co-operation of the medical malariologist, the biologist, the chemist, the engineer and the agronomist. Rural malaria is closely connected with agriculture and pisciculture.

FASCINE DRAINAGE

For control of malaria in places where larger undertakings necessitating a knowledge of engineering are too costly or not feasible (see p. 189) a method of sub-surface drainage, known as Fascine Drainage, has proved very successful. It was initiated as an antilarval measure by G. Waugh Scott in 1934 at Singei Siput, Federated Malay States, but has since been more widely adopted. At first, short stretches of drains were packed and, the measure succeeding, it was extended to other types of watercourse and later to main ravines. The process is carried out as follows: The drain or stream to be packed is first cleared and deepened and, if necessary, straightened. Then lengths of jungle trees, rubber trees, branches or bamboos are laid longitudinally and are covered with lallang, grass, ataps, etc., and a layer of earth over all.

After as long as six years, both wood and lallang were still in a good state of preservation. It is a known fact that so long as timber is in water and buried well below contact with the atmosphere it will survive for long periods, and these fascine drains are always moist and usually contain running water. The drains must not be too tortuous or choking may occur, particularly in sandy soil. In such soil the drains should be almost perfectly straight, and bamboos are preferable. Another benefit of this fascine drainage is that it prevents erosion and loss of trees on the banks of open drains.

TRANSPORT OF MOSQUITOES, *Anopheles gambiæ*

Increased facilities for travel and increased rapidity of transport introduce fresh menaces of the spread of malaria or of its introduction into places hitherto free from infection, and indicate the necessity for rigorous measures of control. Spread by aircraft will spring at once to mind, but more instructive is the concrete case of the introduction of *Anopheles gambiæ* from Africa to America. *A. gambiæ* was a species peculiar to the continent of Africa, but between August 1928 and

February 1930 it was introduced into the State of Rio Grande do Norte, Brazil. It must have been brought thither, to Natal City near the seashore, by *avisos*—rapid steamers which cross the Atlantic from Dakar to Natal in the short space of three days. Inspection of these *avisos* by officials of the Port Sanitary Department would have prevented the entrance of infected vessels, but they were allowed to slip through. In 1931, in Alecrim district, near the anchoring ground of the *avisos*, a serious outbreak of malaria occurred. There is no need to describe this epidemic in detail; suffice it to say that it surpassed all previous records in the number of sick and the fatality rate in Brazil. This mosquito is dangerous from another point of view also, for it acts as an effective transmitter of *Wuchereria bancrofti*.

This newly introduced mosquito has been found infected to a higher degree than any other local mosquito; Nelson in 1932 found 32 per cent. infected in Natal, Brazil. In 1938, or about eight years after its first introduction into the country, it gave rise to a very widespread outbreak in Rio Grande and Ceará. Some 40,000 persons were attacked, and fully half of them died. During this period of eight years the insect had extended its range to the northern parts of Brazil, and more than fifty localities in the State of Ceará were found infected. It is very widespread in Africa, and, from what is known there, it is argued that it may spread over the whole American continent. Areira Branca, near the seashore, is visited by aeroplanes, and if these are not carefully disinfected they will of a surety play their part in extending the range of this anopheles. In the State of Rio Grande do Norte it breeds readily in sweet water containing *Pistia stratiotes*, and collections of sweet, stagnant and clear water covered by aquatic vegetation, mostly *Pistia stratiotes*, are common there. Other known important breeding sites for this mosquito are the watering-troughs for animals, small pools in drying rivers, olheiros or washing-tubs of wood and clay, or wooden barrels used for irrigation of plants cultivated in the kitchen gardens, slowly moving brooks near human dwellings, and the banks of lakes.

DIAGNOSTIC METHODS, MAINLY SEROLOGICAL

On the question of laboratory methods of diagnosis of malaria (p. 246) investigations have been undertaken in recent years in several directions. In the first place, work has been carried out, mainly by V. Chorine, in an endeavour to ascertain the nature and rationale of Henry's reaction. He has come to the conclusion that it is not due to the presence of antibodies in the serum. Melanin has not the properties either of an antigen or of a toxophore group, except for organisms normally devoid of this pigment. Again, the reaction occurs in distilled water or hypotonic solutions only; this also is unlike the behaviour of antibodies.

The chemical mechanism of the reaction is complex, the chief rôle being played by euglobulins and a positive reaction does not occur unless the euglobulins constitute 32 per cent. of the total proteids of the serum, and if a greater proportion than this is present the intensity of the reaction varies directly with the quantity of euglobulin present. Malarial euglobulins have no special affinity for melanin and differ in no way from

the euglobulins of normal serum. Heating the serum to 55° C. for half an hour abolishes the malaria reaction because carbon dioxide is driven off and the serum becomes more alkaline. The euglobulins are rendered unstable by diluting the serum with hypotonic solutions of ammonium chloride, or by lowering the pH of the serum to near the isoelectric point of globulins.

Wolff has devised a test which is a development of Chorine's modification of Henry's test. Chorine's determination of the distilled water precipitation of euglobulin requires the use of a photometer: Wolff's Buffer Precipitation Test does not. The procedure is one of the standard methods of determining isoelectric points. Stock buffer solutions are prepared. The pH concentrations used by Wolff were 8·4, 8·0, 7·4, 7·0, 6·4, 5·8, 5·4, and 5·0. As the solutions do not keep well in a tropical climate, 0·2 per cent. formalin was added before the final adjustment.

One c.c. of each of the diluted buffer solutions is placed in one of a series of small test-tubes. Two drops of serum are added to each tube; the tubes are shaken and, after being left standing for five minutes, are read. The serum is taken in the early morning before breakfast on the day preceding the test, 3 c.c. of venous blood being placed in a dry centrifuge tube. After the clot has formed and been loosened, the tube is kept overnight in a refrigerator. If the serum is not quite clear it is centrifuged before the test is carried out. Results are recorded as opalescent, faintly cloudy, cloudy or markedly cloudy.

Normal sera rarely show more than a faint cloudiness at pH 7·0, and only an opalescence at 7·4. Strongly positive sera show cloudiness or marked cloudiness up to 8·0, 8·4, and even beyond. Weakly positive sera show cloudiness up to 7·4. The maximum precipitation is not reached at the same pH concentration by all sera. Generally the maximum reached by the negative serum is at a lower pH than the maximum reached by a positive serum. For practical purposes two tubes, pH 7·0 and 7·4 would be sufficient. This Buffer Precipitation Test has been used by Wolff in parallel with the Henry Test on 350 sera, with results closely comparable.

Cutaneous reactions and precipitin tests have proved far from reliable in the diagnosis of human malaria. Hermann and Lifschitz used antigens prepared from blood-clots of malarious patients, but, when tried, such antigens often failed to give rise to cutaneous reactions in infected persons. Sinton and Mulligan used, in monkey malaria, parasites treated with papain, but when the same method was applied to human parasites a high percentage of non-specific reactions was obtained.

Dulaney and Stratman-Thomas have obtained highly specific results to complement fixation tests in human malaria. After many trials they found the best antigen to be one prepared from the laked red cells of monkeys highly parasitized with *P. knowlesi*. The parasites were washed free of hæmoglobin, dried and ground. For use, the product is re-hydrated with physiological saline, frozen and thawed. Antigens have been prepared similarly from human blood infected with *P. vivax* and *P. malariæ*.

The malarial antigen is group-specific and not species-specific.

Either of these antigens gave strong complement fixation with sera of patients infected with any of the types. A further noteworthy point is that the complement fixation with malaria antigen is not modified by pre-existing syphilis, and patients negative to syphilis, but with malaria parasites in their blood, give a negative Wassermann reaction with a 4-plus complement fixation with malaria. The test is closely correlated with the presence of recent presence of malaria parasites in the peripheral blood. But a negative complement fixation test does not rule out the presence of malaria parasites. The test is especially valuable in *P. faciparum* infections, where the parasites appear during the acute clinical attack only on alternate days. The test tends to become more positive as the numbers of parasites in the blood increase, and, as the parasites disappear, the antibody titre of the serum decreases. Seventeen of eighteen cases of induced malaria gave markedly positive complement fixation reactions at one time or other in the course of the disease, and no strongly positive reactions occurred in non-malarious patients.

CHAPTER VI

BLACKWATER FEVER

METHÆMALBUMIN

Pseudo-methæmoglobin was the name suggested by Fairley (p. 270) for a newly discovered blood pigment, formerly confused with methæmoglobin, found in the plasma of blackwater patients. Fairley, carrying out further work on this in conjunction with R. J. Bromfield, found that it is modelled on the methæmoglobin pattern, but that the protein component is native serum albumen instead of native globulin; the iron is held in the trivalent state and is even more resistant to reducing agents than is methæmoglobin itself. For these reasons Fairley has changed the name of pseudo-methæmoglobin to methæmalbumin.

The pigment is derived from circulating extra-corpuscular hæmoglobin liberated during intravascular hæmolysis. What part, if any, it plays in blackwater fever is not known as yet. It occurs in incompatible transfusion, in nocturnal hæmoglobinuria (Marchiafava-Micheli disease) as well as in the plasma of blackwater fever cases. Marchiafava-Micheli disease is characterized by early morning hæmoglobinuria, permanent hæmosiderinuria and the presence of methæmalbumin free in the blood; cell resistance is, however, normal and there is no free hæmolysis in the circulating blood.

Vitex penduncularis

In the section dealing with the history of the treatment of blackwater fever mention was made of *Vitex penduncularis* (p. 277), and it was stated that its active principle had not been isolated. Since then analytical

work on the plant has been carried out, and its use has been further tested clinically.

Vitex peduncularis belongs to the Family Verbenaceæ. In 1924 Chopra, Knowles and Gupta analysed the leaves and found therein an alkaloid. They tested a freshly prepared infusion on patients with malaria, of all three types, but could not confirm that it had any action on the parasites in the blood, nor on the temperature, nor on the clinical symptoms. In short, they came to the conclusion that in malaria it was quite useless. They did not try its action in cases of blackwater fever. J. E. Measham, however, in 1940 (*Indian Med. Gaz.*, 1940, v. 75, p. 25), reported on the use of the infusion in eleven cases of blackwater in the Anamallai Hills whom he had attended between 1936 and 1939. These hills are in the south-western ghats (lat. 10° 20′ N., long. 76° 57′ E.). Of the eleven patients, seven were Malayalese, three Tamils and one European. All but one, a Malayalee of 35 years, were cases of a severe type with high fever, intense nausea, vomiting and jaundice. One had suppression of urine for 24 hours. All were given 1 oz. of the infusion hourly till the urine regained its normal colour; then four times daily for three days. Five had one or two doses of atebrin or quinine, but no more, and six of them had none; one, the European, had a full course of atebrin. The urine cleared on the third day after the infusion was begun, and the general condition improved, though the temperature might keep up for another couple of days. One, a female child of eighteen months, with subtertian rings in its blood, died; the rest recovered. A very striking feature was the rapid disappearance of the severe pains in the liver and loins.

According to Chopra the *Vitex peduncularis* grows in Bihar, Eastern Bengal, and the Central Provinces, and the aboriginal tribes there use it in the treatment of malaria, blackwater fever and kala azar. It is known by the local names of Nagbail, Nagphani, Charaigora, Chhagriaruba, Minjurgorwa, and, in Bengal, as Baruna and Doda. In treatment, the natives use an infusion of the leaves, the root bark, or the young stems.

CHAPTER VII

YELLOW FEVER

Ship Outbreak

The advent of steam-driven vessels reduced the danger of yellow fever outbreaks on ships at sea (p. 291) almost to vanishing point, for mosquitoes would probably be blown away or die in the course of a long voyage—not so in sailing vessels and the old wooden ships with cask storage of water and accumulation of stagnant bilge. In those days, mosquitoes taken on at ports or watering-places would find facilities for breeding on board, and the new brood would infect themselves by

biting the men who had acquired the virus on shore, or from infected mosquitoes taken on board. The *Prince Edward* may be cited as an instance. In 1890, in a voyage from Rio de Janeiro to the Mississippi, she lost four of her complement on account of this disease within the first three weeks. Five weeks after sailing she arrived at Barbados and was quarantined there but not disinfected. Eight men, young Europeans, fresh from England and therefore non-immunes, were signed on to replace those lost, and she sailed to Ship Island, Mississippi, reaching the quarantine station three and a half weeks after leaving Barbados, but no further cases occurred either on the voyage or on arrival. There must have been infective mosquitoes on board at the start of the voyage from Rio, or non-infective mosquitoes and one of the crew at least in the first three days of his attack. Failure of more cases to develop, in spite of the presence of non-immune members among the crew, points to death or disappearance of the infected mosquitoes.

YELLOW FEVER IN BRITISH GUIANA

When speaking of yellow fever in British Guiana (p. 298), we noted that the disease had reappeared there in 1938, after the lapse of half a century of freedom from infection. We may take it as certain that its endemicity in the colony is now confirmed. In 1940 Dr. P. A. T. Sneath reported that in the preceding year he had taken blood from over five hundred persons in the hinterland, the ages of the subjects ranging from infancy to adult life. He had a few months previously recorded that among 289 persons living or working in the sparsely settled areas of the interior—especially the northern and central Rupununi district—43·5 per cent. were immune to yellow fever. In his later report Sneath states that 185 were immune, by the mouse protection test, out of 506 whose sera were tested, that is 36·5 per cent. The detailed table given below shows the steady increase from early adolescence. The fact of some of the very young proving positive indicates that yellow fever is endemic in the hinterland of this Colony.

Age-group.	No. tested.	No. immune.	Percentage.
1–5	14	2	—
5–10	16	4	—
10–15	62	11	17·7
15–20	64	17	26·6
20–30	161	55	34·2
30–40	89	36	40·5
40 up	100	60	60·0

CRYPTIC YELLOW FEVER

Again, 'silent areas,' or regions of cryptic yellow fever, have been shown by immunity tests for retrospective diagnosis to exist in the Anglo-Egyptian Sudan (p. 413). Atkey, in the report of the Yellow Fever Commission in the Anglo-Egyptian Sudan, found that in four years, from 1935 to 1939, the proportion of natives whose blood gave positive protection tests had risen from nil to 18 per cent., in spite of the

fact that during this period there had not been a single clinical case of yellow fever reported and *Aëdes ægypti* is almost absent. This is suggestive of the existence of yellow fever in the jungle form (p. 423). Recent records have proved, however, that the disease has no longer remained latent, and a serious outbreak of an epidemic character occurred in the Nuba Mountain district of Kordofan Province. Till 1940 no case of yellow fever had been recognized there on clinical grounds. In October of that year, however, over an area of some 6,000 square miles there were 15,000 recognized cases, and 1,600 of these were fatal, in the course of two months.

TRANSMITTERS OF THE VIRUS

We have seen that Aëdes is the commonest transmitter of yellow fever virus which conveys the infection by its bite, and also that other species of mosquito, though their bite is not infective, retain the virus in their bodies and can by injection or inoculation (such as would be brought about by crushing the insect caught biting and by rubbing in the infected body) cause disease. The list of insects which have been proved capable of transmitting the virus by their bite has been shown to be fairly large. F. G. Sarel Whitfield in an article on *Air Transport, Insects and Disease*, published in 1939, gives the following (p. 1115), in which the insects are named in chronological order of their being reported.

LABORATORY INFECTION

Instances of laboratory infections by yellow fever (p. 400) have reached a total which can no longer be regarded as negligible, namely thirty-seven. In every instance there had been close contact with material containing either the virulent pantropic or the neurotropic strains of virus, and the portal of entry was either skin, conjunctiva or nasopharyngeal mucosa. Other, non-human, cases, however, are more puzzling and are not so readily explained. Thus Findlay and MacCallum report that two monkeys, *Macaca mulatta*, developed 'spontaneous' yellow fever at an interval of seventy-one days and both died from the infection. They were in separate animal houses; no other monkey infected with yellow fever had been in the same room for three and six months respectively. No pantropic virus was in use in the laboratory during these intervals. The method of infection was not discovered. Mosquitoes were absent, but monkey-lice and rat-fleas, *Ceratophyllus fasciatus*, cockroaches, *Blatella germanica*, and a small ant, *Monomorium pharaonis*, were present.

Findlay and MacCallum made further tests to ascertain whether any of these might have been the vector responsible. Experimental introduction of the virus of yellow fever into the stomach of *Macaca mulatta* and of *Cercopithecus æthiops* was followed in two or three days by appearance of the virus in the blood-stream. In man, the acid gastric juice inhibits the virus in less than fifteen minutes. In the case of the monkey the food is in a firm pultaceous mass, and it is probable that either the virus passes rapidly through the gastric mucosa or soon enters the duodenum, whose contents have an alkaline reaction. Perhaps

Insect.	Distribution.	Habitat.	By whom and when reported.
Aed. lutcocephalus Newst.	W. Africa; S. Sudan	Tree holes, cut bamboos	Bauer, 1928
Aed. stokcsi (apico-annulatus), Evans	W. Africa; Uganda	Tree holes, cut bamboos, banana stumps	Bauer, 1928
Erctmopodites chry-sogaster, Graham	Tropical Africa	Tree.holes, banana stumps, tins, large fallen leaves	Bauer, 1928
Aed. scapularis, Rond.	S. America	Ground pools, temporary rain pools, salt marshes	Davis and Shannon, 1929
Aed. albopictus, Skuse	Orient generally	Tree holes and domestic	Dinger *et al.*, 1929
Aed. vittatus, Bigot	Mediterranean, Africa, India	Rock pools, gutters, drains	Philip, 1929
Aed. africanus, Theo.	Tropical Africa	Tree holes, bamboo stumps, semi-domestic	Philip, 1929
Aed. simpsoni, Theo.	Tropical Africa	Tree holes, leaf axils, etc.	Philip, 1929
Mansonia africana, Theo.	Tropical Africa	Larvæ and pupæ attached to Pistia roots and other aquatic plants	Philip, 1930
Aed. fluviatilis, Lutz	S. America	Ground pools	Davis and Shannon, 1931
Aed. tœniorhynchus, Wied.	Central and S. America	Rock holes along stream-beds	Davis and Shannon, 1931
Culex thalassius, Theo.	Tropical Africa	Coastal marshes	Kerr, 1932
Culex fatigans, Wied.	Tropics and sub-tropics	Domestic	Davis, 1933
Amblyomma cajen-nense	Central and S. America	—	Aragão, 1933
Ornithodorus rost-ratum, Arag.	S. America	—	Aragão, 1933
Ornithodorus mouba-ta, Murray	Africa	Domestic, native dwellings	Aragão, 1933
Stomoxys calcitrans	Cosmopolitan	Manure and debris	Hoskins, 1934
Aed. geniculatus, Oliv.	Europe	Tree holes	Roubaud *et al.*, 1937
Aed. leucocclænus, Dyar and Shannon	S. America	—	*Whitman and Franca*, 1938
Hæmagogus capri-corni (janthino-mys), Lutz	S. America	Tree holes	*Whitman and Franca*, 1938
Aed. triscriatus, Say	N. America (outside endemic zones of yellow fever)	Tree holes, small pools	Bennett, Baker and Sellards, 1939

man could be immunized orally if the gastric acidity could be overcome. Attempts to do so fail ordinarily with the dog, the rabbit, rat, guineapig, mouse, hen and pigeon.

Again, these investigators found that when the virus was injected into the abdomen of the cockroach, *Blatella germanica*, it retained its activity certainly for fifteen days, if the insect was kept at 19° C. They do not suggest that the cockroach plays a part in the epidemiology of yellow fever, but it may be noted that African and South American monkeys eat grubs and insects and, perhaps, cockroaches.

JUNGLE YELLOW FEVER

Cases of the jungle type of yellow fever may start an urban outbreak, and the reasons why this does not occur more often than is actually the case have been noted (p. 426). The opposite of this, however, the start of a jungle type outbreak by a case of urban infection does not seem to occur. Even where jungle extends almost to the confines of a town in which urban yellow fever exists the disease does not spread among those inhabiting the former. The sparseness of the population is, doubtless, one factor in this, but greater, of course, is the absence of *Aëdes ægypti*, and the rate of adaptation—which may be slow—of the virus to other mosquitoes. As evidence that such adaptation is going on we may cite that some jungle mosquitoes, *Psorophora discrucians*, for example, remain infective for eight days only; in Mansonia the virus multiplies, but is not transmitted by the bite of the insect. In July 1938, however, another species of Aëdes, *Aëd. serratus*, was found to be a natural vector in jungle areas where monkeys were found infected in nature.

R. C. Shannon, Loring Whitman and Mario Franca seized the opportunity of an outbreak of jungle yellow fever in Rio de Janeiro in 1938 to collect 24,304 mosquitoes on the spot. Among the many species captured two gave evidence of being natural vectors, namely *Aëdes leucocelænus* and *Hæmagogus capricorni*, since their bites proved infective; *Aëdes serratus* was among those caught, but its specimens proved negative. One or more species of Sabethinæ may harbour the virus, but natural transmission by them was not proved; they conveyed infection only when injected.

Marchoux, Simond and Salimbeni at Rio de Janeiro in 1906 tried to transmit the urban virus by *Aëdes scapularis*, but without success. This is now known to be one of the jungle species which readily infects itself and transmits the infection by its bite. There does not seem to have been any error in the observation of Marchoux and his colleagues, for they allowed the mosquitoes to bite a patient in the early days of his fever and the insects were then kept at 27° C. for thirteen days; four of them were then fed on a non-immune subject who remained well. It was not a case of ' inapparent ' infection because subsequent exposure to an infected *Aëdes ægypti* gave rise to the disease in this man.

India and Yellow Fever

Eastern countries are, quite rightly, running no risks of introduction of the virus of yellow fever, for species of Aëdes, capable transmitters, are known to exist in abundance and a non-immune population is ripe for attack. Rules have been promulgated by an International Sanitary Convention for Aerial Navigation by a Quarantine Commission at Singapore (p. 435), and the Government of India made its Order in 1936 (p. 436), and three years later, in 1939, promulgated the Indian Aircraft (Public Health Emergency) Rules. In the preamble of them is the statement that they have been introduced because the " Central Government is satisfied that India is threatened with an outbreak of yellow fever and that the ordinary provisons of the law for the time being in force are insufficient for the prevention of danger arising to the public health through the introduction of that disease by the agency of aircraft."

By these Rules no aircraft from an infected area may land for the first time in British India except at Karachi. Twenty African territories are listed as infected areas, including Kenya and Tanganyika. No person shall bring into British India an aircraft infected with yellow fever, and aircraft will be considered infected if there is, or has been, a case of yellow fever on board: if the aircraft has not been disinsectized—after landing in an infected area—at Alexandria, Cairo, or Khartoum, with Pyrocide 20 in a prescribed manner; or if there is on board any person who has been in an infected area within nine days of arriving in India, provided that he has not been protected by inoculation within the preceding two years or by a previous attack of yellow fever.

If, in spite of these prohibitions, an infected aircraft does land in India, measures are laid down for the treatment of the aircraft and passengers.

These Rules, which go far beyond those of the International Sanitary Convention for Air Navigation of 1933, to which India is not a signatory, show that serious apprehension is still felt as to the possible introduction of the disease into a non-immune population in a country with suitable insect vectors and monkey reservoirs. The nine-day time limit, instead of the six days laid down by the Convention, the obligation to disinsectize aircraft in a specific way, and the inclusion of certain territories in the list of infected areas are all controversial points.

CHAPTER VIII

AFRICAN TRYPANOSOMIASIS

Reservoir Hosts

Evidence of the thoroughness and excellence of Bruce's work—though described as Bruce's, the part played by his team of able fellow-workers must not be lost sight of—is found in the fact that most of the propositions laid down by him in 1903 are still valid. One important

dictum, however, has had to be not merely modified but given up altogether, that in which he states (p. 474), "There is no real evidence that any of the lower animals take any part in the spread of the disease." Apart from game and wild animals which have been shown to be reservoir hosts, the native pig has been found by Van Hoof and others in the Congo to harbour *T. gambiense*. The animal may be infected by the bite or may be inoculated experimentally. No reaction is produced in the pig, but it remains infective for at least a year. After cyclical transmission through three pigs in series, flies were allowed to feed upon the pig and then bite a human volunteer. The latter became thereby infected.

DISTRIBUTION AND MEASURES OF CONTROL IN RECENT YEARS

The distribution of sleeping sickness in Africa in 1934–5 has been detailed (p. 491). The state of things four years later has been reported by H. M. O. Lester, of the Nigeria Sleeping Sickness Service. "Most of the Tanganyika Territory," he states, "is infested with tsetse. Sleeping sickness is no longer serious, as the population of infected areas has been concentrated in special settlements. There were only 168 cases in 1937. Cattle trypanosomiasis is the important problem. The fly-free areas are overpopulated and overstocked. Soil impoverishment and erosion are increasing, and will continue to do so unless spread of tsetse is stopped and new areas reclaimed. A cattle assess on the four to five million cattle there would provide funds for soil and grazing control for tsetse research. A cheap and easy method of reclamation, to be used when required, is essential.

In Uganda and the Sudan sleeping sickness is under control. The populations of the old epidemic areas have been removed to less dangerous regions. They are inspected regularly and cases treated. In both countries the restriction of population is causing overcrowding and soil impoverishment. It is hindering development and will have to be reconsidered.

In Nigeria the disease is being controlled by mass treatment, and the establishment of dispensaries, protective clearing by communal labour, and, as a last resource, the movement and concentration of population; 300,000 cases have been treated in the last seven years. In many of the main epidemic areas the infection rate is now a tenth of the old figure. In moving population the object is to secure the maximum improvement and development and to try to make the new settlements demonstrations for the rest of the country. People are being helped to build model compounds, and villages are being laid out properly."

Meanwhile the number of cases in French West Africa remained high. In the Ivory Coast and in Togo old foci continued to be active and the situation was serious. In the Cameroons there remained a state of feeble endemicity and there were only a few epidemic foci. In French Equatorial Africa it was retrogressing, only a few foci remaining, the chief being Haute Sangha and Ouhane. Large numbers were examined in the French West African colonies: 2,977,268 in 1936, and 2,770,574 in 1937. New cases discovered numbered 57,162 and 41,295 respectively and 93,139 old cases were reviewed.

In the French Sudan the disease, in 1939, was mainly affecting the Volta Noire, the Bani and vicinity of Bamaka, portions adjoining the Ivory Coast and French Guinea. In this part, though *G. palpalis* and *G. morsitans* are found, the commonest tsetse by far is *G. tachinoides*.

A brief summary of the work carried out in Northern Nigeria in recent years to deal with sleeping sickness are of interest in bringing the history of the Colony up to date in this respect.

Prior to the appointment of special sleeping sickness officers in 1927 a few hundred cases were treated each year at general hospitals and at Sherifuri. Between 1928 and 1930, officers toured parts of the Northern Provinces, treating such patients as came to them, some 3000 to 4000 a year, but it was difficult for a touring medical officer to stay in any village for more than a short time and few patients completed their treatment.

In 1930 every effort was made to persuade patients to attend regularly for a full course of injections. No attempt was made at compulsory examination, and treatment was voluntary. Towards the end of 1930, the system of compulsory surveys and mass treatment was inaugurated. It soon became evident that a large part of the central region of the Northern Provinces was heavily infected and there were signs that the disease was spreading rapidly. The fact was then realized that, when dealing with hundreds of thousands of cases, the cost of surveying the whole area regularly would be prohibitive; once a mass survey had been accomplished and all cases treated, a field dispensary was established to deal with relapsing patients and those freshly infected. At the same time, adequate protective measures are essential; anti-tsetse clearing by local communities, and in some instances the removal and concentration of the population are the only certain methods of controlling the disease. Though the surveys had not been completed and in other places re-survey was urgently needed, it became clear that up to 1935 the disease was still spreading in spite of all efforts. Since then, however, there has been an improvement, writes Lester in 1939. In 1937 a special Sleeping Sickness Ordinance was enacted to give the necessary legal powers, a scheme for expansion of the Service was approved and a grant of £19,000 a year for five years was obtained from the Colonial Development Fund to pay for a control service. Since then the disease has come much more under control and large-scale protective campaigns have been started to consolidate the gains of recent years.

NEW DRUGS FOR TREATMENT

Neocryl has been reported upon very favourably for treatment of African trypanosomiasis, as being less toxic, better tolerated, and of higher trypanocidal power than tryparsamide (p. 528). After more prolonged observation, however, it has proved to have serious limitations. Ian S. Acres in 1940 reported on a series of twenty-one patients who had been treated with this drug and had been kept under observation for at least two years. He found that patients in the first stage responded well, in fact their condition compared favourably with that of those who had been given tryponarsyl. In the later stages, however,

it proved disappointing. Of twelve patients in the second stage who received the treatment three only were cured. To four relapsed patients a second full course was given but without benefit, and two became unresponsive to subsequent treatment with tryponarsyl; whereas of eight relapsed cases receiving tryponarsyl later, six reacted favourably.

These facts would appear to furnish clinical support and confirmation for the observation previously made by Hawking, Hennelly and Quastel that the trypanocidal activity of the cerebrospinal fluid is less with neocryl than with tryparsamide.

Another compound which has proved effective in laboratory animals—it has recently been tried in human patients—is the aromatic diamidine, diamidino stilbene, $4:4'$–R–CH:CH–R where R is $\underset{\text{NH}_2}{\overset{\text{NH}}{\diagdown}}C\diagdown$, tested by Lourie and York in mice infected with a laboratory strain of *T. rhodesiense*, in doses of 0.01–0.0125 mgm. per 20 gm. weight. The maximum tolerated dose is some thirty times the minimum curative dose. Tests on rabbits in an advanced stage of infection gave results equally good.

J. L. McLetchie has given this drug to several infected persons and found that those who had no marked involvement of the nervous system reacted as effectively as to Bayer 205; the drug was, however, not so useful as the combined Bayer 205 and tryparsamide. R. D. Harding also tried it on human patients in Northern Nigeria. In the mild or moderately severe it gave good results, but in others no improvement was obtained. It has also been tried in the treatment of kala azar (see Chapter IX).

AMERICAN TRYPANOSOMIASIS

Mode of Conveyance

The question of the mode of infection conveyed from the insect vector, whether by bite or by faecal inoculation (p. 535), is still undecided, though opinions are verging more towards the latter view. In 1939, Brumpt marshalled the evidence available and summed up the question (*Ann. Parasit. Humaine et Comparée*, V. 17, 320-31). He pointed out that as long ago as 1912 a *Cercopithecus ruber*, which had resisted numerous bites of *Triatoma megista*, had been observed to develop a fatal infection after the deposit of the excreta of the infected insect on the ocular mucosa. Whilst the majority of observers support the 'faecal' hypothesis, certain workers, notably Mühlens, Dios, Petrocchi and Zuccarini, and Cardoso, have reported that they have succeeded in infecting mice by the bites of infected bugs, after taking all precautions to avoid contamination by the bug's faeces. But the biting parts of one bug might have become contaminated by the faeces of another, or its own. Brumpt points out that cannibalism among them is common, that Mühlens and his collaborators and Cardoso succeeded in infecting only a single animal, and that when they later tried to obtain infections from the bites of the same bugs they failed. Finally, Denecke and

Von Haller, when they took careful precautions to prevent contamination of the mouth parts by infective excreta, failed in a long series of experiments to obtain a single infection by means of the bite.

CUTANEOUS LESIONS, CHAGOMA

￣In the first issue of this work certain symptoms found in cases of Chagas's disease, notably Romaña's sign, cardiac disturbances, and the association of goitre or myxœdema, and their significance were discussed (pp. 540–5). In the past two years considerable attention has been paid to cutaneous lesions and tumour formations in this disease. Salvador Mazza and Gilberto Urcelay—the former being the recognized leading authority on this condition, having for years carried out epidemiological investigations and original studies upon it—have classified the cutaneous lesions of Chagas's disease under six heads: (1) Invasion of the skin itself; (2) Extension to the subcutaneous cellular tissue; (3) Intense involvement of the epithelium with destruction and necrobiosis; (4) Inflammatory cytosteatonecrosis, with leishmanial forms of *T. cruzi* in the fat cells; (5) Centripetal lymphangitis and nodular formations along the paths of the vessels; (6) Sub-epithelial infiltrations with obliteration of the line of distinction of epidermis and corium.

The fourth and fifth of these have been further studied. The name *chagoma* has been given to a tumour formation resulting from cutaneous inoculation of *T. cruzi*, and it may be followed by metastatic swellings spread by the blood-stream. Its characteristic pathological lesion is a fat necrosis of the tissue cells, especially the subcutaneous fat. This fatty necrosis is not a secondary degenerative change but part of the initial inflammatory stage of invasion, and is a manifestation of the colonization of the leishmania forms in the fatty tissue. Cases are related, in children ranging in age from three to twenty-one months, who showed the primary 'inoculation chagoma,' with secondaries two to three months later. Those who received treatment with 7602 Bayer recovered; others who did not died.

An analogous case in an adult is also recorded by Mazza and his colleagues, the patient being a man of fifty years who presented himself with nineteen of these tumours, eighteen of them discovered by palpation, another in the right axilla, harder, firmer and more defined. At first the Machado reaction was negative as was also experimental inoculation into puppies; later, however, both were positive. A biopsy was made of the axillary swelling, and Mazza describes in detail the patholgical histology with illustrations showing invasion of the dermis and the presence of the leishmanial stage of *T. cruzi* in the histiocytes. The patient was given 5 c.c. of 7602, intramuscularly: this was repeated two days later and the swellings were much less marked. Four days later he was given by injection 20 c.c. of a 3 per cent. solution freshly prepared. The tumours then rapidly disappeared. In all, he received 22·2 mgm. per kilogramme.

Mazza has also described certain changes in the liver which he regards as pathognomic of this disease, and he advocates the use of the viscerotome or taking specimens of the liver in doubtful cases. These changes are nodular formations, mostly situated in the middle of the lobules, made up of accumulated lymphocytes in a thick network of reticular histiocytes which dissociate the tissue and appear on section as circular foci. This *nodular hepatitis* with proliferation of histiocytes in an indurated, passively congested liver is, he states, of diagnostic importance. In the same way as the viscerotome has proved its value in the epidemiology of yellow fever, so it is as regards Chagas's disease, by enabling sections of the liver tissue to be made for demonstrating characteristic pathological changes. At the same time as the tissue of the liver is taken, opportunity may be seized to take also a portion of the cardiac muscle to show the presence of the parasite there. Pons reported in November 1939 to Mazza that of the first five 'cardiac viscerotomies' performed, three, all of the patient's children, had revealed the characteristic findings of Chagas's disease.

CHAPTER IX

LEISHMANIASIS

Adler's experiments led him to conclude that human and canine leishmania were strains undergoing evolution under differing circumstances, rather than different, clearly defined species, and that the dog might be a reservoir of the human virus (p. 558).

E. Sergent and his co-workers in 1939 noted that the Mediterranean kala azar seemed to be transmitted by *Phlebotomus perniciosus* from dog to dog and from dog to man rather than from man to man, the dog being the principal reservoir. This belief acted upon in Canca, Crete, where in 1933 destruction of dogs was followed by lowered incidence of kala azar, as recorded by Papantonakis, whereas Sergent found that reduction of the human reservoir by treatment of all discoverable cases had not resulted in lowering of incidence.

Treatment

The variability of the fatality rate according as proper and timely treatment is undertaken or not is well exemplified by two epidemics which were occurring in the fourth decade of the present century. There is a tribe, the Dinka tribe, living to the west of the White Nile and some hundred miles north of Malakal. An outbreak of kala azar started there in 1932 and lasted for eight years. Among the population of 8000 there were at least three hundred cases and 240 or more deaths occurred—an 80 per cent. fatality rate. The type was acute, and by

the time the patients were admitted to hospital the disease was advanced and death took place in spite of treatment.

A happier record comes from the Province of Bihar, in the hospitals and dispensaries of which 92,000 cases of the disease were treated in 1937, and 95 per cent. were cured among those receiving thorough treatment (reported by S. L. Mitra, 1938).

Diamidino-stilbene (4: 4'-diamidino-diphenyl ethylene), the use of which has been mentioned in the treatment of African trypanosomiasis (see appendix, p. 1120), has also been tried for human cases of kala azar, after success has been observed in laboratory experiment. W. Yorke and A. R. D. Adams have reported on a few cases, and L. E. Napier and G. N. Sen on a larger number (*Indian Med. Gaz.*, December 1940). Though the total of patients so treated is at present small, the general conclusion is that it is an effective therapeutic agent in this disease. A dose of 1 mgm. per kilo injected intravenously daily for 8 to 12 days is generally advised, and a cure is effected with a total dose of less than one gramme per 100 lb. body-weight (the mean relative total dose in seven successful cases was 0·795 gm. per hundred pounds). Adults appear to tolerate well a single dose of 0·0005 gm. per lb. body-weight and, by gradual increase, double this can be tolerated. Ill-effects—flushing, burning sensation, vomiting, cardiac failure—are immediate but transitory, and, though alarming, are not dangerous, and are relieved almost at once by adrenalin which, in those who seem to be very susceptible, may be used prophylactically in a dose of 0·125 c.c.

CHAPTER X

LEPROSY

LEPROSY IN EUROPE

Though it is not within the scope of our programme to speak in detail of the existence and prevalence of leprosy in the colder countries of Europe, conditions in Iceland, Norway and parts of Russia were mentioned (p. 581-3). The subject, however, merits a little fuller notice than the few words given to it, and no reference at all was made to Germany.

Mediæval West Pomerania extended from what is now known as the River Ryck, near Greifswald, to the border of Mechlenburg, and it included the island of Ruegen. Pooth has studied the question of leprosy in this district, and tells us that from the thirteenth century there were leprosaria in the towns and countryside of the mainland and on Ruegen. As elsewhere, in the earlier days the lepers of a town, excluded from civil and social life, would settle outside the city walls and depend for subsistence on charity. Again as elsewhere, they did so well that others joined them till they formed a community and the

town council had to provide for their orderly administration. New buildings were erected, usually with a chapel attached, and admission depended on payment of a fee, but there were funds to pay for those too poor to do so.

Dr. Oberdoerffer, who has lived in Griefswald and made investigations there, conjectures that the population in the thirteenth to fifteenth centuries was not more than 80,000 and nineteen leprosaria are named as existing at that time, and he thinks that the incidence was about 5 per mille. In Northern Germany it was the custom to dedicate the chapels of the leprosaria and the institutions themselves to St. Juergen (St. George), and wherever there is a St. Juergen church or village it is more than likely there was formerly a leprosarium. From records which Oberdoerffer can trace of leprosaria becoming transformed into monasteries or almshouses in so short a time as fifty years it must be inferred, as elsewhere, that these houses were not reserved for lepers but were probably inns for travellers, and, by inference, the number of lepers in the buildings was probably not so high as five per mille, or four hundred interned. The latter figure, if correct, would lead us to expect at least twice that number of cases in all. We may call to mind in this connection W. P. MacArthur's words in his *Notes on Old-time Leprosy in England and Ireland* (see p. 573).

Prevalence in Africa

Some figures later than those given (p. 586) of the prevalence of leprosy in Africa were published by Muir in January, 1940, in a special African number of the *Leprosy Review.* The following summarizes the state of things at that date: The disease is common in all parts of Africa except in dry deserts inhabited by nomadic tribes. In Southern Central Africa it is most common in the hot low-lying moist areas along Lake Nyasa and in the Zambesi basin, open lepromatous cases preponderating in the former, but the total number of lepers being greater in the latter. In South Africa a severe type is seen in Europeans though the frequency of the disease is decreasing among them. Good progress has been made since the compulsory system has been modified to allow uninfected and recovered patients to be released. All contacts of admitted lepers are now examined regularly in order that early infections may be detected. The Emjanyana Leper Institution in the Transkei is now so popular that more than a third of the admissions are voluntary and the patients insist on treatment. The number of cases in the South African institutions has varied during the past twenty years only from 2265 to 2374, but by June 1938 there had been 4502 discharged, though kept under observation for several years, and 2738 had been released from such surveillance as having recovered.

Basutoland has also had a compulsory system, one feature of which is the training of leprosy inspectors to search out cases. In other British areas of Africa the financial position precludes compulsory segregation, but the work, in Nigeria especially, shows that a great deal is being done at small expense through the co-operation of missions with the Government. The Uzuakoli Leper Settlement has recently extended its work by establishing clinics in the neighbouring villages;

in short, leprosy relief work is being gradually extended over an ever-widening area and at low cost with the help of the Native Administration and the British Empire Leprosy Relief Association.

PREVALENCE IN THE EAST

Opportunity may be taken to add a few words on more recent returns of prevalence in other countries. Thus, J. Lowe, after a tour of Burma, reported in 1938 an incidence rising to as high as 5 per cent., and among them a greater preponderance of serious lepromatous cases than is found in India. Also, that in Burma the disease is more severe in the indigenous people than in the Indians, even when the latter have contracted it in Burma. The disease develops at an earlier age in the Burmans. Lowe suggests that since the Burmans are better fed than the Indians the lack of resistance among the former is more likely to be explained by hereditary or racial tendency or susceptibility.

Formosa (p. 592), according to available evidence, was infected from China some three hundred years ago, and within the succeeding century the disease gained a firm foothold. In 1736 an institution known as Yohsai-in was founded for segregation and relief of lepers in Shokwao owing to prevalence of the disease. Later, other benevolent institutions for the care of lepers were established.

At the present day, apart from those mentioned below, it is estimated that there are about " a thousand open cases of leprosy dangerous to public health " (Kamikawa). In 1929 an Anti-leprosy Law was promulgated in Formosa providing for compulsory segregation or home isolation under strict control. There is a Government Leprosarium, the Rakusei-in, at Shinso Guai, Taihoku Prefecture, about eleven kilometres from Taihoku city. When first opened in 1930 it accommodated a hundred patients, but it has been much enlarged since and now has a capacity for seven hundred. Also near Taihoku city at Hachiri Sho, is a private institution, the Rakuzan-in, for sixty patients. Three hospitals—the Mackay Memorial Hospital in Taihoku, the Shinroh Hospital in Tainam, and the Christian Hospital in Shokwa—treat out-patient lepers in small numbers once or twice a week. Lastly, since 1938 the Anti-leprosy Association of Formosa, a semi-official organization, has assisted in carrying out measures suggested by the Government. It conducts a home for the uninfected children of lepers, engages in antileprosy education of the public, and gives advice to those infected.

A report by Dr. Cilento on conditions in Australia (p. 594) has brought our knowledge down to more recent times. In a paper contributed to the *International Journal of Leprosy* in 1939, Cilento wrote of leprosy in Queensland at that date. A Health Act of 1937 had given new powers to examine suspects and contacts. An enquiry in a northern area revealed a focus of fourteen clear and twenty-five suspected cases, and every infected family was thereafter examined every three months for new cases. Between 1925 and 1938 fifty-eight whites and seventy-one aboriginals have been found infected, and 126, of whom eighty-eight were males and thirty-eight were females, have been admitted to the Pearl Island Lazarette. The number of new detections in the five years 1931-5 was more than double that found in any of the six previo ·

five-year periods; the increase was due mainly to newly discovered cases among the coloured population.

As regards Western Australia, leprosy is found only in the warmer northern part, where an enquiry into its incidence was made in 1937–8 by Dr. A. P. Davis. Most cases were found in the northern Kimberley division, fewer in the north-west. In the former, forty-two cases were found among 4001 examined; in the latter two among 1690. The disease is said to have been introduced by indentured labour of the pearling industry. The number of notifications in the West Kimberley division rose from two to seven in the years 1908 to 1932 to forty-one to fifty-eight in 1933 to 1936. The condition is said to be now under control, and in 1937 the new notifications fell to nineteen in 1937.

Prevalence in the Western Hemisphere

Let us now turn to the western hemisphere. Colombia is believed to have been free until the disease was brought in by Spaniards coming over from Andalusia, and later by slaves imported from West Africa. A lazaretto was established at Cano de Loro in 1795 with patients transferred from Cartagena; another, Lazaretto de Contratación, was founded in Santander in 1861, and that of Agua de Dios in the Department of Cundinamarca in 1870. In these are housed 8200 lepers. A census in July 1938 showed that there were 2341 children under five years of age living with their leprous parents, 1193 in Contratación and 1148 in Agua de Dios, just over 30 per cent. of the leprous population of these places.

In 1940 there were in Contratación: (1) The Guadelupe preventorium, for 250 to 350 healthy children of lepers. In 1938 there were 257. (2) The San Bernardo preventorium, inaugurated in April 1936 for 250 healthy children. Today there is accommodation for 400, and at times it is full. As an annex to this is (3), a *crèche*, which in March 1939 had forty-three infants. More *crèches* are in contemplation to house infants born of leper parents so that they may be cared for from the very beginning.

Leprosy Control in India

The story of leprosy control in India (p. 615) has some historical interest. In 1887 the Government of India thought that efforts should be made to control leprosy, and they accordingly set about to obtain information as to the number of leprosy institutions, numbers of inmates, rules as to separation of the sexes, and other matters. The number of institutions was small, and they were mostly temporary halts for vagrant leper beggars. It was decided in 1888 that to stamp out the disease the sexes should be separated and all lepers should be confined for life. This, of course, was out of the question, and the only practicable measure appeared to be to give medical and charitable relief in voluntary hospitals and asylums.

The following year, however, the Legislative Department prepared a draft bill for compulsory detention of all vagrant lepers, and correspondence on this resulted in the appointment of a commission " to

investigate the problem of leprosy in India " (p. 621). This consisted of five members, three selected in England by officials of the National Leprosy Fund (a memorial to Father Damien who had recently died in Hawaii) and the Royal Colleges of Physicians and Surgeons, and two by the Government of India. The three former were Dr. Beaven N. Rake of Trinidad, Dr. G. A. Buckmaster and Dr. A. A. Kanthack, and the two from India were Surgeon-Major A. Barclay and Dr. S. J. Thompson. The first-named alone, Dr. Rake, had had any experience of leprosy, and he was a man with pronounced anti-contagionist views, and he first cleared the board by ruling out all cases in an endemic area, on the grounds that such had no evidential value.

The findings of the Commission were: (1) That leprosy was neither syphilis nor tuberculosis, but had analogies with the latter; (2) That leprosy is not transmitted hereditarily, and the disease tends to die out because the majority of lepers are sterile; (3) That it is contagious and inoculable, but is not spread widely by these ways; (4) That leprosy is not peculiar to any race or caste, nor does it arise from the use of any particular food, nor by reason of any climatic or telluric conditions; (5) That poverty, bad food and insanitation predispose to it; and (6) That it arises *de novo* under a combination of conditions whose inter-relation is not known.

Consequently, the Commission did not recommend segregation, absolute or partial, but advocated voluntary isolation. Their recom-mendations comprised: (1) Prohibition of the selling of food and drink by lepers, and of their engaging in ' contact ' occupations, as bakers, washermen, etc. (2) Discouragement of concentration of lepers, by prohibiting vagrant lepers from begging, from using public conveyances and from frequenting places of public resort. Lepers infringing these regulations were to be placed in asylums which should be built near towns to receive them.

As a result of this we have the peculiar condition of things that the disease is contagious to an " exceedingly small degree," nevertheless voluntary isolation, prohibition in engaging in certain trades' and occupations, control of movements, and establishment of asylums are recommended for dealing with it.

The Government of India nevertheless adopted the report, and on it was based the Leper Act of 1897, clearly framed with a view of deferring to public opinion (that leprosy is contagious) and mitigating a public nuisance. This is a permissive Act which can be enforced by local governments by notification.

Cultivation of *Mycobacterium lepræ*

On the vexed question of the cultivation of the organism of leprosy there is another recorded success which, however, awaits confirmation. It is of some historic interest and therefore must be mentioned. It is that of Professor F. Lleras Acosta of Bogotá, who in May 1933 announced that he had succeeded in cultivating on Petragnani's medium an acid-fast bacillus obtained from the blood of patients with nodular leprosy. From this he prepared a methylic antigen in the same way as Boquet and Nègre from *Mycobacterium tuberculosis*. Acosta carried

out complement fixation tests with sera from 638 cases of clinical leprosy confirmed bacteriologically and found 634 (99·3 per cent.) positive; of 360 macular or maculo-anæsthetic cases, but not confirmed bacteriologically, 333 (92·5 per cent.) were positive; among 211 sera of children of lepers living with their parents thirty-nine (18·4 per cent.), and among the same number of children living away from their parents in leper colonies twenty-four (11·3 per cent.) were positive. Among 160 considered (by a Medical Board) as cured, sixty-one (31·8 per cent.), among 264 with diseases other than leprosy four (1·5 per cent.), and among 1194 healthy subjects one reacted positively.

A. Saenz in 1938 reported that he had obtained and cultivated an acid-fast bacillus from tap-water which was indistinguishable from that of Lleras Acosta and which gave the same reactions as other para-tuberculous saprophytes, but P. C. R. Pereira tested Acosta's reaction on 120 patients with cutaneous leprosy and found 117 positive sera (97·5 per cent.); also twenty-six out of thirty-two (81·2 per cent.) of lepers bacterially negative, in four among 100 children of lepers, in fourteen of seventy-six (18·4 per cent.) with syphilis or other skin affections, and in seven of fifty (14 per cent.) healthy subjects. These show considerable differences when compared with Acosta's records.

S. H. Black and H. Ross tested the reaction in 164 positive (nodular ?) and twenty-four negative (neural) cases, and 329 suffering from diseases other than leprosy, and fifty tuberculous patients and obtained positive results in nine out of the twenty-four neural cases—the form in which the diagnosis is often in doubt and the test, if true, consequently of the greatest value—and in 10·3 per cent. among the non-tuberculous controls. They do not therefore regard the test as of much value in diagnosis.

Lleras Acosta also claimed that intradermal injection of 'leproline' made from his cultures gave a reaction in healthy subjects but not in lepers, indicating immunity in the latter. This also will be of value, if confirmed.

CHAPTER XI

CHOLERA

BEAUPERTHUY'S VIEWS

Beauperthuy's views on the causation and transmission of cholera should be mentioned for two reasons: First, because he was a man of repute for his powers of observation (we have seen that he was one of the first to suggest the mosquito transmission of yellow fever—see p. 356); secondly, because his views are on record in his works at the French Académie des Sciences, and one cannot help wondering what can have been the basis for his extraordinary statements in regard to cholera.

Epidemic cholera, according to him, is caused, or is trasmitted from

the sick to the healthy, by one of the Hemiptera—an Acarus, in fact—which he describes in detail. This inserts its sting (aiguillon), which is situated at the end of the hind legs, into the skin and subcutaneous tissues causing no more pain than does a mosquito bite, although the fineness of the sting lets it penetrate more deeply, and in pricking it introduces the poison of cholera. A single prick is not enough to set up fatal disease, but " the repeated pricks of several cholera insects " cause symptoms the severity of which depends on the number of pricks and the site of attack. These symptoms, moreover, are very similar, he maintains, to those following stings by scorpions or centipedes, or the bites of snakes: numbness of lips, tongue and limbs, giddiness, tinnitus, vomiting, diarrhœa, chills, dim vision, diplopia, bleeding from the mouth, ecchymoses, and, in pregnant women, abortion. The insect comes out at dusk and is nocturnal in its habits; it settles on the exposed parts of the body and arms, choosing especially the backs of the hands. At first its movements are sluggish, but as darkness deepens it becomes more lively and pricks repeatedly and deeply if the subject is asleep. It attacks not man only, but animals, domestic and other, which accordingly also suffer from cholera. In 1854 at Cumana, states Beauperthuy, cholera killed fowls, parrots, fern-owls, monkeys, pigs, goats, dogs, and even donkeys, after they had exhibited nausea, vomiting, diarrhœa, cramps, tonic contractions and paralysis. In India the bodies of the dead which the natives cast into the Ganges breed the cholera insect.

Beauperthuy argues from this that cholera is not a contagious disease, but, if preventive measures are to be effective, the cholera insect must be kept out by fumigation of houses and its importation from other countries must be guarded against by quarantine of vessels. With the discovery of steam and increase in the number of steamships " it is impossible today," he writes, " to forestall the ravages of this scourge, and the insect threatens the destruction of the human race." He goes on to prove his point by saying that the earth over cholera bodies buried without coffins sinks and contains holes passing down to the abdomens of the dead. These are not due to the escape of gases of putrefaction, for they pass vertically, are of equal diameter throughout, and, in short, are clearly the work of boring insects. If, however, they had penetrated from without down to the body, there would be, around the openings, signs of the soil removed, but there are none. They must, therefore, have bored their way out from within, and the hollow of the soil over the abdomen is due to the falling in of the earth as the insects make their way out, " a fact of great importance and one which throws light on the mode of extension of the insect which produces cholera."

It is indeed a matter for wonder that such a fantastic theory should be put forward and still more strange that it should find support. That it did is clear from letters dated October 1855 and January 1856, which accompany Beauperthuy's book which is entitled *Travaux Scientifiques de Louis Beauperthuy*, and may be consulted at the library of the Académie de Médecine.

Beauperthuy, of whose views many thought highly, does not really seem to have been in advance of his time. He was forestalled by Nott in the idea of the mosquito transmission of yellow fever; his notions on the transmission and epidemiology of cholera, given above, are ludicrous

and fantastic, and he held that leprosy was also due to inoculation of a virus by an "Acarus resembling the *Pediculus pubis*." Dr. de Brassac, who wrote an introduction to Beauperthuy's book, says: "I stayed with Dr. Beauperthuy for four months and repeatedly asked him to show me his Acarus, but he has never given me that satisfaction;" he ends with these words: "Une seule chose doit sauver le Docteur Beauperthuy d'une jugement trop sévère, c'est désintéressement." No more need be said.

<p style="text-align:center">OUTBREAKS 1937-39</p>

Since the last outbreak mentioned in Wu Lien Teh's list, that which affected Hong Kong, Canton and Shanghai (p. 664) there has been an epidemic, in 1937-8 at Tonking and north Annam. The infection was introduced by Chinese entering clandestinely into Tonking. The epidemic really consisted of two outbreaks, the first from September to December, 1937, and, after a lull, in September and October, 1938. Altogether there were 20,027 cases and 14,921 deaths, a 74·5 per cent. fatality rate.

For prophylactic purposes for contacts and others at risk a vaccine was prepared at the Pasteur Institute, Dalab. Nearly 25,000 litres were prepared, comprising six milliard (6000 million) organisms per cubic centimetre. A single injection of 2 c.c. was given because the population was a scattered one and there was difficulty in assembling them for a second injection. The vaccine proved harmless and the results were excellent. No case occurred, for example, among coolies employed on night-soil removal, nor in the hospitals among the nurses, nor among the grave-diggers. A curiosity worth noting was the case of a man who died with choleraic symptoms after getting himself fraudulently vaccinated seven times on the same day in order to sell the vaccination certificates.

A concrete instance of water-borne cholera (see p. 671) in recent times deserves mention by reason of the thoroughness with which its investigation was carried out. Details are given in a Report of the League of Nations Epidemic Commission to China by Robertson and Pollitzer of investigations undertaken in the provinces of Hunan, Hupeh and Kiangsi in 1938.

Importation of cholera into Shanghai from an indentified focus in the mid-Yangtse basin had been suspected for some years. This focus proved to be the valley of the Yuan which enters the Yangtse through the Tung-ting lake. This lake is a large sheet of water and acts as a reservoir to the flood waters of the Yangtse Delta where the river passes into the lake at Changteh.

There was an epidemic at Changteh in December 1937 and January 1938, with fifty cases; in February there was none, in March one, but from April that year till January 1939 there was an epidemic in Hunan and the adjacent provinces traceable to the Yuan River valley. Water used for making tea was boiled, but raw water was taken for drinking, for washing vegetables, for cleaning dishes and for general household purposes. Pedlars would sprinkle fruit and vegetables with the river water to keep them fresh. Junks were stationed at anchor round the jetties, but the crews used the river as their latrine. The night soil was collected in barges above the site of water collection. The regular

sewers were covered, but in Yuanling there were small heavily polluted brooks running through the city. The river water was the main source of infection and a vicious circle was set up, the river itself being again polluted. Agglutinable vibrios were isolated from the river water. It is clear, therefore, that the possible sources were three: the habit of the junk crews urinating and defæcating into the river; collection of human night soil in barges for export to farmers in rural areas; and, perhaps the chief, the habit of washing night soil containers in the river after the contents had been emptied into the barges.

Flies played some, but probably only a small part; food was undoubtedly responsible at times. The disease declined with the termination of the water-melon season. This fruit was cut into portions and the slices exposed for sale, being kept fresh by covering them with rags, usually filthy, dipped in the polluted water of the river.

Water-borne traffic was one of the chief means of spread and infection was often carried up-stream.

Statistics regarding this outbreak are probably not very accurate, but they may be given here as some indication of the prevalence. At Hunan, to the end of August 1938, there were 4547 cases and 1792 reported deaths (39·4 per cent. fatality), but the fatality rate was very variable. At Changsha Hospital there were 409 cases and 64 deaths, or 15·6 per cent. At Changteh Hospital, in April 20 cases 11 deaths, in May 63 cases and only 9 deaths. In May, Rogers's treatment was instituted: hypertonic saline was given for the first injection, normal saline with one per cent. glucose for the subsequent injections if such became necessary. The reduction in the fatality rate for May is clear. In August, among 150 cases only 11 were fatal (7·3 per cent.) in the hospital, but 25 deaths occurred among 31 patients who did not enter hospital.

PILGRIMAGES AND CHOLERA

Another, probably less well known, instance of spread of cholera by food and personal contact (see p. 669) may be mentioned, namely the annual feast and celebration to Nuestra Señora de Paz y Buen Viaje, held at Antipolo in Manila. Large numbers of devotees, 10,000 or more, congregate there and may remain for weeks. Food is brought from .infected houses and districts outside, and generously shared. Patients in the early stage might freely intermingle, and excreta disposal left much to be desired; pilgrims would bathe in Mariquina River after visiting the shrine, and, further down, others would drink the water. Cholera would spread locally at Antipolo and about Luzon, then in all the surrounding districts radiating from the centre at Antipolo. Others who escaped the local infection would perhaps stop at Pasig and partake of vegetables which were being fertilized with human excreta.

CHOLERA, EL TOR AND OTHER VIBRIOS

Marras's conclusion regarding the adequacy of serological tests to distinguish *Vibrio choleræ* from cholera-like vibrios, especially El Tor (p, 679) is not borne out by the findings revealed in an investigation of

the outbreak in South Celebes in 1938. Clinically the symptoms were those of true Asiatic cholera, and the outbreak lasted for six months. De Moor gave details of 48 patients. When the vibrio which was isolated was found to hæmolyse sheep's red corpuscles, doubt arose as to its being the true cholera vibrio, for the conjunction of a hæmolytic vibrio with epidemic cholera—the case mortality was 65 per cent.—was a new event. Culturally and serologically the vibrio was an El Tor vibrio which, in spite of its close relationship to *V. choleræ*, has hitherto been regarded as practically non-pathogenic.

De Moor has summarized the many contributions on the El Tor pathogenicity question, which has been the subject of controversy since 1905. When first isolated its hæmolytic power was weak, but its identity does not seem to have been in any doubt. De Moor thinks it possible that on this account (weak hæmolysis at first) El Tor vibrios may have caused other epidemics and been given rank as cholera vibrios.

Continuing the subject, R. Gispen has studied the specific relationships of cholera, El Tor and Celebes vibrios. Examination of two of the Celebes (Macassar) strains confirmed that they are identical with the specific El Tor vibrio. El Tor agglutinable vibrios are possessed of an exohæmolytic action on goat's blood in bouillon, while cholera vibrios show under the same circumstances only an endohæmolytic action. It has been shown also that both cholera and El Tor vibrios possess the same polysaccharide, but the former possesses protein I and El Tor protein II. An examination of 81 strains of cholera and 31 strains of El Tor for the Voges-Proskauer reaction gave 76 cholera strains negative and 22 El Tor positive. So far, it seems that hæmolysis of goat's blood in bouillon and the Voges-Proskauer reactions are the only practical means by which the two vibrios can be distinguished.

Gispen describes a third test reaction, that to heat. Cholera vibrios in saline suspension are rendered inagglutinable by heating at 56° C. for three hours; that is to say, the suspension is no longer rendered clear by the anticholera serum. An El Tor suspesnion, on the other hand, is not affected in its agglutinability. Celebes vibrios behave like El Tor vibrios. A temperature of 60° C. is necessary to destroy the agglutinability of these two latter vibrios. The conclusion is reached that in general characters and chemical structure the El Tor vibrio occupies a position intermediate between the cholera vibrio and the non-agglutinable vibrios, and that the two vibrios, though identical in antigenic structure, do represent different species.

PROPHYLAXIS. QUARANTINE BOARD OF EGYPT

In dealing with the prophylaxis of cholera we mentioned the National Quarantine Service of China and the rules promulgated by it (p. 700). It is probably less well known that in Egypt there is a Quarantine Board which was first appointed by reason of an outbreak of cholera and has been carrying out its functions for more than a century. The Board held its final session on October 31, 1939, and the Government took over its duties. It may be of interest to recall a few of the

main incidents during the hundred and nine years of the Board's existence.

Prior to the reign of Mohammed Ali, the Great, there apparently did not exist any public health service in Egypt, but in 1825 Mohammed Ali called in Clot Bey, who organized a General Council of Health, which included Crete and Syria in its sphere of activity. The sanitary measures then customary in Europe were introduced and quarantine restrictions were thus first operated in Egypt.

When cholera appeared in August 1831, Mohammed Ali convoked the Consular Body in Alexandria and formed a Public Health Service. This body held its first meeting on 8th October, 1831, and the minutes of this meeting are in existence.

After various changes of name, a General Council of the Sanitary Service was formed in 1859 as a result of the Second International Sanitary Conference, the first of such conferences having been held in Paris in 1851. The opening of the Suez Canal in 1869 necessitated a great extension of the activities of this Sanitary Council, and Sanitary posts were established in Arabia and down the Red Sea. Ten years later cholera spread from the Hejaz into Europe *via* Turkey, and plague was epidemic in the Middle East. After a period of financial embarrassment, the International Hygiene Conference at Paris in 1878 set up the Sanitary Maritime and Quarantine Board of Egypt in its present form, the first meeting being held in January 1881.

The International Sanitary Conference in Venice in 1892 drew up a decree which regulated the affairs of the Egyptian Quarantine Board till the present date. In 1894 a conference was held in Paris for the purpose of regulating the Pilgrimage and the El Tor Quarantine Station. Further Sanitary Conferences were held in Venice in 1897 and at Paris in 1903, 1912, 1926 and 1938.

The Quarantine Board had powers and duties to take preventive measures against the introduction of epidemic disease into Egypt and foreign countries; to codify Quarantine Regulations and to apply them; to establish and maintain hospitals for infectious disease; to guard sea and land frontiers from the health point of view, and, later, the airports; to administer the funds of the Board. The sanitary control of the Canal and of the Mecca Pilgrimage was its special task, and the first regulations concerning the Pilgrimage were formulated at a conference held at Constantinople in 1886.

In 1928, in execution of Article 7 of the International Sanitary Convention of 1926, the Regional Bureau of Alexandria was set up for the exchange of epidemiological information among neighbouring countries. It is claimed that the El Tor Quarantine Station succeeded in preventing the extension of four epidemics of cholera between 1907 and 1912.

CHAPTER XII

PLAGUE

VIEWS ON PROPHYLAXIS IN THE FOURTEENTH CENTURY

Attempts to limit extension of the infection of plague in the pandemic of 1346, known generally as the Black Death (see pp. 704-6) were made by isolating infected houses. Thus, it is said that " Milan, by a rigorous barricado of three houses in which the plague had broken out, maintained itself free from the Great Mortality " for a considerable time, and many instances are recorded of the preservation of families by strict separation. Möhsen states that in the middle ages it was common to barricade the doors and windows of houses infected with plague and to suffer the inmates to perish. It is to be feared, however, that the isolation was often evaded without the knowledge of the watcher (see p. 748).

Jacob Francischini de Ambrosiis in the appendix to the *Istorie Pistolesi*, in Muratori, quotes a document put forward authoritatively by the medical faculty of Paris—probably the most celebrated at that time—who had been commissioned to give their opinion as to the causes of the pandemic and to suggest a régime for those threatened with infection. It is worth quoting as an example of what was deemed the highest opinion of the day but which seems to us now meaningless jargon and comprises apparently reasonless directions for prophylaxis.

" We, the Members of the College of Physicians of Paris, have after mature consideration and consultation on the present mortality, collected the advice of our old masters in the art, and intend to make known the causes of this pestilence more clearly than could be done according to the rules and principles of astrology and natural science; we, therefore, declare as follows:

" It is known that in India, and the vicinity of the Great Sea, constellations which combated the rays of the sun and the warmth of the heavenly fire, exerted their power especially against that sea, and struggled violently with its waters. Hence, vapours often originate which envelope the sun, and convert his light into darkness. . . ."

At that day physicians—and, in fact, all men of learning—were convinced of the influence of the stars on outbreaks of disease. In the case of the Black Death, according to Guy de Chauliac, the chief cause was the grand conjunction of Saturn, Jupiter, and Mars, in the sign of Aquarius on 24th March, 1345; secondary to this were " the diseased state of bodies, the corruption of the fluids, debility and obstruction " whereby " the quality of the air and of the elements was so altered that they set poisonous fluids in motion towards the inward parts of the body, in the same manner as the magnet attracts iron; whence there arose in the commencement fever and the spitting of blood; afterwards, however, a deposition in the form of glandular swellings and inflammatory boils." This does not afford much enlightenment to readers

of today, but, writes Hecker, " Herein the notion of an epidemic constitution was set forth clearly and conformably to the spirit of the age."

The Medical Faculty of Paris goes on to say:

" These vapours alternately rose and fell for twenty-eight days; but, at last, sun and fire acted so powerfully upon the sea, that they attracted a great portion of it to themselves, and the waters of the ocean rose in the form of vapour; thereby the waters were, in some parts, so corrupted, that the fish which they contained died. These corrupted waters, however, the heat of the sun could not consume, neither could wholesome water, hail, or snow, and dew originate therefrom. On the contrary, this vapour spread itself through the air in many places on the earth, and enveloped them in fog.

" Such was the case all over Arabia; in a part of India; in Crete; in the plains and valleys of Macedonia; in Hungary, Albania and Sicily. Should the same thing occur in Sardinia, not a man will be left alive; and the like will continue so long as the sun remains in the sign of Leo, on all the islands and adjoining countries to which this corrupted sea-wind extends, or has already extended from India. If the inhabitants of those parts do not employ and adhere to the following, or similar means and precepts, we announce to them inevitable death—except the grace of Christ preserve their lives.

" We are of opinion that the constellations, with the aid of Nature, strive, by virtue of their divine might, to protect and heal the human race; and to this end, in union with the rays of the sun, acting through the power of fire, endeavour to break through the mist. Accordingly, within the next ten days, and until the 17th of the ensuing month of July, this mist will be converted into a stinking deleterious rain, whereby the air will be much purified. Now, as soon as the rain shall announce itself, by thunder or hail, every one of you should protect himself from the air; and, as well before as after the rain, kindle a large fire of vine-wood, green laurel or other green wood; wormwood and chamomile should also be burnt in great quantity in the market-places, in other densely inhabited localities, and in the houses. Until the earth is again completely dry, and for three days afterwards, no one ought to go abroad in the fields. During this time the diet should be simple, and people should be cautious in avoiding exposure in the cool of the evening, at night, and in the morning. Poultry and water-fowl, young pork, old beef, and fat meat in general should not be eaten; but on the contrary, meat of a proper age, of a warm and dry, but on no account of a heating and exciting nature. Broth should be taken, seasoned with ground pepper, ginger and cloves, especially by those who are accustomed to live temperately, and are yet choice in their diet. Sleep in the daytime is detrimental; it should be taken at night until sunrise, or somewhat longer. At breakfast, one should drink little; supper should be taken an hour before sunset, when more may be drunk than in the morning.

Clear light wine, mixed with a fifth or sixth part of water, should be used as a beverage. Dried or fresh fruits, with wine, are not injurious; but highly so without it. Beetroot and other vegetables, whether eaten pickled or fresh, are hurtful; on the contrary, spicy pot-herbs, as sage or rosemary, are wholesome. Cold, moist, watery food is in general prejudicial. Going out at night, and even until three o'clock in the morning, is dangerous, on account of the dew. Only small river fish should be used. Too much exercise is hurtful. The body should be kept warmer than usual, and thus protected from moisture and cold. Rainwater must not be employed in cooking, and everyone should guard against exposure to wet weather. If it rain, a little fain treacle should be taken after dinner. Fat people should not sit in the sunshine. Good clear wine should be selected and drunk often, but in small quantities, by day. Olive oil, as an article of food, is fatal. Equally injurious are fasting and excessive abstemiousness, anxiety of mind, anger, and immoderate drinking. Young people, in autumn especially, must abstain from all these things, if they do not wish to run a risk of dying of dysentery. In order to keep the body properly open, an enema, or some other simple means, should be employed, when necessary. Bathing is injurious. Men must preserve chastity as they value their lives. Everyone should impress this on his recollection, but especially those who reside on the coast, or upon an island into which the noxious wind has penetrated."

Other opinions of the time seem to have had some reason at the base and to have been less hazily expressed. Thus, Gentilis of Foligno, a teacher of Perugia, upheld Galen and Arabian physicians in believing that a ' pestilential atmosphere ' led to corruption of the blood in the lungs and heart, and so invaded the whole body. Rational treatment, therefore, must be based upon a purification of the air by blazing fires of odoriferous wood with, of course, purification of the blood by bleeding and purgatives. He believed in the danger of infection by contact: " Venenosa putredo circa partes cordis et pulmonis de quibus exeunte venenoso vapore, periculum est in vicinitatibus."

THE NEAPOLITAN DISEASE OF 1528

No little dispute has taken place concerning the nature of the disease which attacked and almost annihilated the French army at the siege of Naples in 1528. Everything seemed to favour the besiegers—three thousand veterans investing a city blockaded by the Genoese galleys of Doria and deprived of water when Lautrec turned off the aqueducts of Poggio Reale.

In seven weeks all that was left of the invading host was a few thousands of cadaverous figures incapable of bearing arms. In less than four months from the beginning of the siege it was raised, Lautrec having died a fortnight before, and the wreck of the army retreated, many were captured, and only a few lived to see France.

Fruit was abundant, but other food was scarce; diarrhœa (perhaps

this was dysentery) broke out, the fields became flooded by overflow of the water cut off from the town, fogs arose, the soldiers became bloated and pallid, and, by the middle of July, two and a half months after the start of the siege, the army, as an army, ceased to exist.

The facts were too meagre and too vague to enable us to make a diagnosis of the nature of the disease with any certainty. It has been called ' petechial fever '; it has been said to be plague arising from infected sick soldiers sent out from the city to convey the disease to the besiegers; " the same attempt at infestation," writes Hecker, " had been already made often in earlier times," but he gives no instances. Prudencio de Sandoval calls the disease ' las bubas,' which must not be taken without question as meaning bubonic plague. The term was used for syphilis, like the French vérole (pox) and the German ' französiche Pocken,' and Sandoval seems more than once to confuse ' petechial fever ' and lues. The French called the disease ' les Poches ' (some say after the village of Poggio), a name which is not likely to have been given to so well known a disease as bubonic plague.

LONDON IN 1665

Referring to the Great Plague of London of 1665, Hodges in his *Loimologia* has given a description of the appalling state of things in the city at that time. In the months of August and September, he states, three, four or five thousand died in a week. In another place, Evelyn says, under date September 7th, " Neere 10,000 now died weekly." Hodges gives an account of the first appearance of the infection at the start of the outbreak in these words:

> " Towards the close of the year 1664, two or three persons died suddenly, attended with symptoms that plainly manifested the nature of the disease; hereupon some timid neighbours moved into the city, and unfortunately carried the contagion with them, and, for want of confining the persons who were first seized, the whole city was in a little time irrecoverably infected. . . . It seems quite ascertained that it was imported into London by goods from Holland, brought thither from the Levant, and first broke out in a house in Long-Acre, near the end of Drury Lane, where those goods were carried, and first opened. Two Frenchmen dying, the family endeavoured to conceal it, but it spread from that house to others, by the unwary communication with those who were sick; and infected the parish-officers who were employed about the dead: it went on, and proceeded from person to person, from house to house."

PLAGUE IN KENYA

The prevalence of plague in Kenya has been referred to (p. 719), but in the light of later investigations, carried out in 1939, the relationship of field rodents to plague in Kenya will have to be reconsidered. The question of sylvatic plague (see p. 743) is a serious one for the health authorities. There are two points to consider, the second arising only

if the answer to the first is positive. Firstly, is plague common, or even present to any degree, among the field rodents of Kenya ? If it is, what is its importance for plague in man ?

A high mortality was observed among rodents in the Rift Valley coexisting with outbreak of disease among sheep. This was known to be, not plague, but Rift Valley fever. Bacteriological examinations carried out over a period of years have not proved that any wild rodents are naturally infected with plague in this district.

In 1930–1 field rats were dying in the Nairobi district in large numbers and 2750 were examined—*M. coucha*, Arvicanthus and Otomys —but plague infection was not confirmed in any, nor were their fleas, *Ctenophthalmus cabirus* and *Dinopsyllus lypusus*, proved positive, though in the area of the epizootic. Moreover, these fleas are averse to feeding on man; *X. cheopis* and *X. brasiliensis* in the hut rats were shown to be vectors.

PLAGUE IN THE BELGIAN CONGO

Since the first issue of this work more has been found out regarding the disease in the Belgian Congo. Examination of cases of human plague there in 1938 revealed that the flea there, Ctenocephalus, though a bad vector, provided two strains of the plague organism. Other strains were obtained from fleas of this species caught in the dust of native huts. Altogether thirty-one strains were isolated from fleas of various species. *X. brasiliensis, Ctenocephalus canis,* Sarcopsylla, Ctenophthalmus, *X. cheopis,* twenty-five from rodents, Mastomys, Leggada, Agricanthus, Lemisconys, Lophuronys, and eighteen from man.

J. van Riel and G. Mol wrote in 1939 an interesting article on plague in the Lake Kivu district in the Belgian Congo, near the borders of British territory. To the west of it lies Lake Victoria and to the north-west Uganda. They think that the focus of plague discovered in 1897 by Koch and Zupitza round Lake Victoria may represent " the last trace of the disease from which the pandemics of ancient Egypt took their origin." They elaborate this view for modern times by saying that " Periodically in Uganda and the neighbouring territories of Kenya and Tanganyika this focus shows renewed activity and becomes the place of origin of a devastating epidemic."

PLAGUE IN THE UNITED STATES OF AMERICA

The history of plague in California (p. 721) presents many points of interest. Though, of the United States, it is the one to show most cases, it cannot, nevertheless, be said to have suffered at all severely. Except in 1907 when the total reached 178 there have not been more than 41 reported in any single year, but the disease was present in the State each year from 1900 to 1937. Its first appearance was on 6th March, 1900, when a Chinese was found dead of plague in the Chinese quarter of San Francisco, the nature of the infection being proved by bacteriological examination and by animal inoculation. As is known to occur elsewhere, so in San Francisco, it is possible that plague had

been present, perhaps for weeks or even months, among the rats. Infection may have been introduced from Hong Kong, or, some think, from Honolulu. As occurred elsewhere with yellow fever, there was in San Francisco considerable reluctance to acknowledge the existence of plague, and the work of control was in no small degree hampered by the opposition of the press, " public officials, influential private citizens and even the courts " (Brock C. Hampton). This opposition ceased on the publication in 1901 of a report by a commission of experts appointed by the Surgeon-General of the United States Public Health Service. In successive years the numbers of cases recorded were 22, 30, 41, 17, 10, and of deaths 22, 26, 41, 17 and 8, or 120 cases and 114 deaths. Though the authorities have gone to much trouble to obtain as accurate figures as possible, there is great probability that some deaths and still more cases in the Chinese quarter of San Francisco escaped notification.

From February 1940 to May 1907, the year following the town's disastrous earthquake and fire, San Francisco was again visited by plague. A sailor was taken to hospital from a tug and died from the disease. No other case was seen for three months, but during August there were fourteen attacked and in 1907 there were 178 notifications in California and 87 of the cases were fatal; by June, 1908 San Francisco had had 159 cases, 77 deaths, and this time the disease spread beyond the confines of the 'Chinese quarter and cases were reported from localities outside the town—twelve in Oakland, three in Contra Costa County, and one in Berkeley. The following year the disease was proved to exist among ground squirrels in Contra Costa County.

Plague first appeared in Seattle, Washington, in October, 1907. Whether it was introduced from San Francisco or from Hawaii and the Orient is uncertain. In favour of the former is the fact that there were quarantine restrictions to protect Seattle from Oriental infection, but San Francisco had been infected in 1900 in spite of these restrictions. In favour of the latter is the fact that cargoes from the Orient were generally more rat-attractive than those from San Francisco, and rat infection is known to have remained in Seattle for the succeeding decade without record of any human case. Between 1908 and 1914 scattered cases were seen in various parts of California—in San Francisco five, in Contra Costa six, in Oakland three, and in Los Angeles one—and rodent infection in rats and ground squirrels in several counties.

The next outbreak reported was in New Orleans in 1914, where from 21st June to the 8th September there were 30 cases, 10 of them fatal. Infected rats had been found there two years before. The city was thereafter free till 1919–20 when another outbreak occurred, twenty-two persons were attacked and eight died. In 1919 pneumonic plague was reported from Oakland, California, thirteen cases being notified. The first was a man who had been hunting squirrels on the 11th and 13th August, and was taken ill two days later. This was the first ' pneumonic ' outbreak reported in the United States, although isolated cases of this type had been observed in the first San Francisco outbreak. In 1920 the disease invaded other States: In June to August there were ten cases and three deaths in Pensacola, Florida; and between mid-June and mid-November eighteen cases, twelve fatal, in Galveston, Texas; and from June to August fourteen with six deaths in Baumont,

Texas. For the ensuing four years only a stray case here and there was notified, but in 1924–5 Los Angeles was the scene of another outbreak. In just over nine weeks from 1st November there were thirty-three cases of the pneumonic type, of which only two survived, and eight of the bubonic form, three fatal. Introduction from abroad was more or less ruled out by the fact that examination of the rats of San Pedro, the harbour of Los Angeles, revealed none infected; the rats and ground squirrels of Los Angeles itself were proved to be infective, and to the north of Los Angeles there was, the same year, a severe outbreak among the latter; further, in parts of the city these rodents and the rats were in contact and, finally, the pulmonary affection was held to indicate the ' marmot ' type of plague.

During the ensuing fifteen years in all the United States fifteen cases only were recorded, six fatal, and of these fifteen, eleven, five of them fatal, occurred in California. Of the remaining four, one, a fatal case, occurred in Oregon (1934), two in Utah (1936 and 1939), and one in Nevada (1937). The eleven in California were seen in nine different counties—namely, Los Angeles (2), Monterey (2), Contra Costa, Santa Cruz, Santa Barbara, Tulare, Sonoma, Placer and Fresno, one each.

To sum up: From 1900, when plague first appeared in the United States, to the end of 1939 there were 499 cases and 314 deaths. These occurred in eight States: California 392 cases, 265 deaths, first appearance in 1900, last in 1937; Louisiana 56 cases, 21 deaths, first in 1914, last in 1921; Texas 33 cases, 19 deaths, all in 1920; Florida 10 cases, 4 deaths, in 1920; Washington 3 cases, all fatal, in 1907; Utah 2 cases, both recovering, one in 1936, the other in 1939 (the last human case reported in the United States); Oregon one, a fatal case, in 1934; and Nevada one, non-fatal, in 1937.

PLAGUE IN CENTRAL AND SOUTH AMERICA

As regards South and Central America, rat plague existed in Chile from 1930 to 1932, and the last human epidemic occurred in 1930. An analysis of epidemics of past years shows that, once started, the epidemic flares up and is followed in successive years by outbreaks of less and less intensity until, in some localities, there is complete disappearance. The epidemic, however, in its acute form reappears again and the same subsequent annual decrease takes place. The rat plays the preponderant rôle as reservoir in inter-epidemic periods and may also carry on the infection from one locality to another. But this does not explain the recurrence in cycles of acute epidemics. Macchiavello has come to the conclusion, in confirmation of the work of Long in Peru, that it is due to a reintroduction into the country. The vector in this reintroduction is the plague flea brought to ports in bales of jute from India. A murine epizootic is started and then the human epidemic.

A sudden outbreak in Riobamba, a town in the province of Chimborazo, in the Andes region of Ecuador, when sixteen cases of pneumonic plague occurred within a week, led to special investigations. Suarez found that in these sparsely populated regions both the rat and the flea ordinarily concerned in the transmission of infection are wanting. Nevertheless

plague is endemic, and epidemic outbursts, sometimes characterized by throat symptoms, make periodic appearance. Examining individuals in contact with plague patients, Suarez discovered *P. pestis* in smears from their throats, identified by cultivation and inoculation. He deduces that in populations where such latent cases occur in man the prophylactic measures should include special examination for, and treatment of, these human carriers.

Moll and O'Leary, writing on the history of plague in the Americas, remark on the peculiar absence of the disease from certain parts, such as Colombia, the Guianas, Central America, Haiti and the Dominican Republic, though no satisfactory explanation of the freedom of these places from infection is forthcoming at present. Plague was easily eradicated from Cuba, Mexico, Porto Rico, Panama and Uruguay, though, again, the reason for its ready expulsion from these countries, when it is found almost impossible to clear others, is far from obvious. Mexico, the West Indies, Chile, Paraguay and Uruguay are now apparently free.

In the Argentine the disease, when it first broke out, was not recognized, and even later its existence there was discredited owing to vigorous opposition on the part of the authorities, the press and the public. *X. cheopis* is the predominant flea, but the prevalence has fallen from 95 to 65 per cent. Rural plague was known in 1905, associated with the *cui*, a small Argentine rodent of the hamster type; the name includes *Microcavia australis* and *Graomys griseoflavus*.

Bolivia was the last of the American countries to be invaded by plague, possibly on account of its isolated landlocked situation. In fact, man himself is believed to have been the chief transmitting agent, through the custom of holding wakes over the dead and of sharing among the relations the dead man's blankets, clothing and effects.

POSSIBILITY OF AVIAN TRANSMISSION

A mode of indirect transmission from rodents (see p. 742) has come up for discussion recently. W. L. Jellison (*Public Health Reports*, 1939, No. 19) discusses the possibility of predatory and scavenger birds transmitting plague. Some of them live on rodents; the booby owl occupies the same burrows as the ground squirrel and is its constant companion. Predatory birds may transmit flea-infested rodents and may also serve as accidental hosts of rodent fleas. Further, the fæces of birds which had been fed on plague-infected guinea-pigs were found experimentally to be infective. All this is rather general, but it opens up a possibility as to mode of conveyance of infection to a distance.

SYLVATIC PLAGUE

The study of sylvatic plague (see p. 743) in Mendoza by J. M. de la Barrera has brought out some interesting facts. The 1937 outbreak of pneumonic plague in Mendoza, a province of the Argentine, induced the legislature to pass a measure for the study, first of the mode of preservation of the organism of sylvatic plague in the interval between one

epidemic and another, and, secondly, the rôle played in infection by the domestic rat. An extensive survey was begun of rodents and their ectoparasites. In the course of this work a new rodent was discovered in the nitre regions. This has been named *Tympenoctomys barrerai*; it is somewhat larger than the Graomys.

The relations of rural plague with the rat were specially studied and the former conclusion was confirmed, that sylvatic rodents had little contact with the domestic rat. This accounts for the comparative absence of human plague though there may be a widespread epizootic in rural districts. It has arisen at places far distant from one another and where importation was not possible. It must have persisted as enzootic. Sylvatic plague is not merely a rodent infection; it is also a flea infection. With the diminution of the flea index in summer and the diminution of rodents by death in an epizootic, propagation of the disease becomes increasingly difficult and plague remains latent by reason of the reduction of acute cases.

Although sylvatic plague may not be accompanied by much human disease, its existence is nevertheless a danger, for, if there is an abundant harvest of maize, there will be an increase of sylvatic fauna, contact between them and the plague-carrying Rattus is facilitated and the access of plague to man becomes easier.

Plague Vaccines

An interesting series of experimental studies on *P. pestis* and plague vaccine and its preparation for personal prophylaxis (see p. 763) has been recorded recently by Sokhey (in 1939). He found that addition of defibrinated blood, copper sulphate and sodium sulphite promotes growth on agar surfaces, perhaps because of the reducing power of these substances. Viable organisms were counted by the number of colonies produced by making progressive tenth dilutions of the bacterial suspensions and planting 0·05 c.c. of a sutable dilution on 40 sq. cm. of blood-agar and incubating at 37·5° C.; the best dilution for enumeration is one giving ten to forty discrete colonies. Standard conditions necessary are the use of equal quantities of the same nutrient broth, the same amount of inoculum, test-tubes of the same internal diameter, a vertical position and undisturbed state in the incubator. By these means a constant infective dose can be determined, the white mouse acting as a constant and highly susceptible animal. The wild house-rat, the white rat and the guinea-pig give too wide limits. The first of these might need anything from 800 to 85,000 organisms; the second 40 to 8500, and third six to fifteen million or more, whereas ten organisms were found to kill all white mice.

Measurement of virulence has always been difficult to assess. Sokhey's standard is the determination of the smallest number of organisms which, subcutaneously administered in doses of 0·2 c.c. of a dilution of a 48-hour broth culture, incubated at 25° to 27° C., to a batch of inbred white mice, will kill practically all of them within 3 to 11 days. The relative virulence of different strains might be gauged by the average number of days elapsing between infection and death. He has found that the following is a simple and convenient method of

maintaining the virulence of cultures. The strains to be preserved are planted on 5 per cent. rabbit-blood agar slopes in test-tubes, incubated at room temperature (26° to 32° C.) for four days and then sealing the tubes in the flame and storing them at 4° to 2° C. By this procedure cultures have retained their virulence unchanged for certainly three years.

Otten's Living Vaccine (p. 763). H. J. Rosier reported in 1938 that in the preceding three years more than six million inoculations had been given in Java and that in 1937 nearly two million (the figure given was 1,804,234) inoculations of Otten's living vaccine were injected—most of them reinoculations. He attributes the steady decline of plague largely to the vaccination campagin, but it must not be forgotten that the long-term policy of building out the rat is being continued at the same time.

In December 1940, Professor Otten himself published a comprehensive article entitled *Het levende pestvaccin en zijn resultaten* (1935–9) [" Results of Living Plague Vaccine, 1935-9 "], dealing with the whole subject. The original article is very detailed; the chief points have been summed up by W. F. Harvey for the *Tropical Diseases Bulletin*, from which the following is taken. The article is divided into three main sections dealing respectively with experimental investigations, plague vaccination, and preparation of the vaccine.

Early experimental work on the dead plague vaccines gave sometimes satisfactory results, sometimes negative results, whatever vaccine was used—Haffkine's bouillon, the German agar vaccine, or Flu's phage vaccine. This led the author to conclude that it was not the particular type of vaccine that was responsible for the variation, but the particular species of animal used in the testing. The domestic rat is the least susceptible to plague infection and the guinea-pig the most susceptible. It appeared also that the grade of susceptibility and the degree of immunity which could be reached were highly correlated, so that the domestic rat, mouse, house rat and guinea-pig form an ascending series as regards possibility of immunization. The outcome of these researches convinced Professor Otten of the impossibility of attaining a satisfactory immunity with dead vaccine in the house rat and the guinea-pig and led him to diverge to the trial of living vaccine. An accidental isolation of a strain of plague from a dead rat accelerated the research and culminated in the advocacy of the use of living plague vaccine for human prophylactic inoculation. This was the famous ' Tjiwidej ' strain which, after preservation in deep stab serum-agar at 5° C. for four months, was found to be avirulent. Even in doses of 5 c c. of a bouillon culture, or a whole agar culture, it proved harmless to house rats and guinea-pigs. Nor was this avirulent condition altered by passage through animals. What was still more important, however, was the next finding that the new strain was not merely avirulent, but was highly and effectively immunizing even in the very susceptible test animals the house rat and the guinea-pig. This proved to be the case not only for artificial infection but for infections contracted under more natural conditions, such as by blocked flea transmission the vaccinated animals showed a high degree of survival to the flea infection, in marked contrast with the non-vaccinated controls.

Life-History of Relapsing Fever Spirochætes

In connection with the life-history of relapsing fever spirochætes in the tick Boné's recent work should be cited. He has carried out an interesting series of investigations to determine the actual mode of conveyance of infection by the tick. For his observations he studied *Spirochæta duttoni* and *Ornithodorus moubata*. The ticks were kept usually at 30° C., after having been fed on mice with numerous spirochætes in their blood. Four out of five mice injected with the coxal fluid emitted by the ticks when feeding became infected. Further, actual spirochætes were seen by dark-ground examination in twelve out of fifteen specimens of the fluid, the interval between the infective meal and the examination varying from seven days to six months. With regard to the salivary glands and possible infection from them, numerous experiments with ticks infected both hereditarily and by feeding on infected blood gave uniformly negative results, and Boné concludes that the usual mode of infection when a tick feeds is by excretion of the coxal fluid containing spirochætes. The secretions from the Malpighian tubules also failed to produce infection with ticks four days to four and a half months after they had fed on infected blood. The granules present in these tubules are found in non-infected ticks and are not believed to have any connection with the spirochætes.

Boné also studied the evolution of the spirochætes in the body of the tick and found that when ingested the organisms rapidly passed through the stomach wall without undergoing any intracellular life-cycle, and appeared in the hæmocele. The spirochætes multiply in the blood of the tick and generally make their way to the coxal glands where they accumulate in the interior. Spirochætes were also found in a certain percentage of the eggs laid by infected females, but inoculation of mice with emulsions of such eggs only occasionally infect mice. It may be that the coating with the egg contents reduces the virulence for mice, but this is conjecture.

CHAPTER XV

MELIOIDOSIS

Later Cases

To the list of recorded cases of melioidosis (pp. 801–2) there may be added the five reported in 1939 in Indo-China by Alain and Delbove; three of the patients were natives and two were Europeans. The latter are worth mention because of the unusual symptom of the passage of dysenteric stools which formed an outstanding clinical feature. Both the European cases were in children. One was a girl of four years suffering from fever and diarrhœa with glairy blood-stained stools, to

the number of thirty in the 24 hours. The child's condition became gradually worse, with insomnia, prostration, and at times delirium. Six days after admission to hospital she complained of pain in the parotid region. A blood culture yielded a growth of *Pf. whitmori.* Death took place two days later.

The second was a boy only two years 'of age, also with diarrhœa. His blood contained *P. falciparum.* Four weeks after admission to hospital without apparent cause, the child showed the same symptoms as the last—glairy, blood-tinged stools and fever (39° to 40° C.). Ten days later there developed a left-sided parotitis; blood-culture.gave a growth of *Pf. whitmori.* Death occurred in another ten days. The first patient came from Nha-Trang, southern Annam, and the second from Bac-Lieu, in Cochin-China. In neither case could any source of infection be discovered.

THE PLAGUE OF ATHENS

The question whether the Plague of Athens (430 B.C.) might have been an outbreak of melioidosis or of tularæmia has been discussed (pp. 805 *et seq.*). Recently, another suggestion has been put forward by T. J. McKinney that it was measles attacking an unprotected community. Points which he mentions as favouring this diagnosis are the sudden onset, the eye symptoms, the sneezing, the hoarseness and cough, the enteritis, the rash and the subsidence of the fever in seven to nine days; the loss of memory being due, possibly, to encephalitis. On the other hand, pustular and ulcerating lesions and loss of fingers, toes and genitalia are not seen in measles.

The same writer makes another suggestion—smallpox. In favour of this are the sudden onset, the rash, the pustules and the ulcers. On the other hand, in smallpox the primary fever is over in three days, the secondary rise of temperature occurring with the pustulation. Further, catarrhal symptoms are not a characteristic feature of smallpox.

It must not be forgotten that the two diseases may occur together, as at the time of the outbreak usually accepted as the first appearance of measles in Europe—in France during the Saracen invasion. The first recorded epidemic of measles in Brazil, in the sixteenth century, was also associated with smallpox.

CHAPTER XVIII

AMŒBIC DYSENTERY AND HEPATITIS

CULTIVATION OF *E. histolytica*

Though ascribing the actual cultivation of the entamœba of dysentery to Boeck and Drbohlav in 1924 (see p. 831), we feel that it is only right to mention that in the opinion of many *E. histolytica* was cultivated on

artificial media *in vitro* by D. W. Cutler of Manchester, England, in 1918. He used a whole egg medium to which few drops of blood were added, or a blood-clot medium which gave equally good results and had the advantage of being clear. Cutler seeded his medium with fresh dysentery fæces and incubated at 28° to 30° C. Growth was maintained by frequent subculture. He produced dysentery in cats by rectal injection of his cultivated amœbæ, and also by feeding them with the cysts which were obtained by ceasing the sub-culturing for three or four days and then placing the material in the ice-chest for a couple of hours.

Cutler's observations were not universally accepted, but there seems to be no valid reason for doubting his claims. Boeck and Drbohlav's method was more successful than Cutler's, but they used a medium closely similar, so that their results should strictly be regarded rather as confirmatory of Cutler's than as an original accomplishment.

Diagnosis by Laboratory Methods

We are glad of this opportunity of rectifying an omission from the first issue of this work and thereby doing justice to the researches of Colonel C. F. Craig, of the United States Medical Service, who has contributed, among many other things, much to our knowledge of the diagnosis of amœbic dysentery by laboratory methods, and, in particular, the complement fixation test. The developments of this branch of the subject—diagnosis by laboratory methods—are distinctly of historical importance.

G. Izar in 1914 stated that he had obtained complement fixation in human cases and in kittens experimentally infected, using as antigens an aqueous extract of fæces and of the pus from an hepatic abscess. In the ensuing six years little or nothing was done on this aspect of the subject. Then, in 1920, von Hage, though following Izar's methods, was unable to confirm the latter's results. In the succeeding year, I. Scalas, an Italian, recorded positive findings from the use of a watery extract of the entamœba-containing mucus of a dysentery stool. During the next six years the question seems to have been in abeyance, at all events no papers are to be found dealing with it until C. F. Craig wrote on the subject in 1927 and repeatedly in the next seven years, during which time confirmation of its value was afforded by Spector, Menendez, Heathman, Sherwood, Tsuchiya, Weiss and Arnold.

There is no need here to give details of the test; it is analogous to the Wassermann test, except that for antigen an alcoholic extract of cultures of the entamœba is used, growth being obtained on a modified Boeck-Drbohlav medium, and a human hæmolytic system is employed, using Group I (Jansky) individuals because the corpuscles of members of this group are not acted upon by the isohæmolysins in any of the four human groups.

Of the value of the reaction there can be no doubt; the following is Colonel Craig's account of the results of his first thousand tests:

" Of the thousand individuals tested and checked by stool examinations, 175 or 17·5 per cent. gave a positive result, and 825 or 82·5 per cent. gave a negative result with this test. Of the 175

individuals giving a positive reaction, *Endamœba histolytica* was found in the fæces of 157 or 89·7 per cent. In those patients giving a positive reaction in whom the stools were negative, but one or two stool examinations were possible, so that it is probable that had a greater number of stool examinations been made the agreement between the results of the test and the presence of *Endamœba histolytica* would have been greater. Of the eighteen cases in which the parasites were not found in the fæces, seven were individuals having indefinite intestinal symptoms, while in eleven a diagnosis of chronic ulcerative colitis had been made."

In cases of acute amœbic dysentery the test is not needed, for fæcal examination is quicker and simpler, but for detection of carriers and of amœbiasis (apart from dysentery), or where fæcal examination is not feasible, the test is of great diagnostic value.

Modifications of Craig's original method have been suggested, notably that of Tsuchiya (who inoculates a medium of nutrient broth, starch, charcoal and Dorset's egg with washed Entamœba cysts to obtain a suitable antigen) and that of Weiss and Arnold which aims at increasing the sensitivity of the test. There will doubtless be others, but, historically, the important point to record is the original idea.

CHAPTER XIX

TROPICAL DISEASES CONNECTED WITH FOOD

In speaking of the treatment of Infant Beriberi mention was made of an alcoholic extract of white rice polishings in Manila under the name of tiqui-tiqui (p. 892). Another preparation recently introduced and employed with success is thiamin chloride. This is identical in chemical form with natural vitamin B_1. The question of dosage is not settled because there is at present no accurate method of determining the degree of deficiency in the patient. The range is expressed in International Units of which 300 are equivalent to 1 mgm. of thiamin chloride. Infants are given 100–150 I.U.; children of two to eight years 150–200, from eight to fifteen years 210–300; adults 300–500, and women in pregnancy and lactation 400–600 I.U. Conrado Mata gave an account of children so treated in 1939. Tiqui-tiqui had been given from birth, but had not prevented the onset of the disease; striking improvement had followed parenteral administration (subcutaneous, intramuscular or intravenous) of thiamin chloride. In infant beriberi it should, he recommends, be taken by both the mother and the child and be continued throughout the first year of the child's life.

SHOSHIN AND BERIBERI

Apart from, or at all events not altogether identical with, the wet form of beriberi (p. 896) is the condition known as ' Shoshin.' This is a

name given, in certain parts of China, to an acute cardiac condition, so acute that it is really a medical emergency. It is not seen in those patients in whom nerve symptoms develop early because the latter necessitate complete rest. The symptoms are of comparatively sudden onset with distressing dyspnœa; the patients are intensely restless, with violent palpitations, præcordial discomfort to agonizing pain, and they toss from side to side without relief; respiration is frequent and shallow, the expression is one of anxiety, the pupils are dilated. If untreated, the patient dies with intense dyspnœa, but usually retains consciousness to the last. Vitamin B, in appropriate doses brings about speedy cure; usually some 3000–5000 I.U., intravenously or intramuscularly, are needed for the initial dose.

EPIDEMIC DROPSY.

In the list given (pp. 902–3) the last outbreaks referred to are those of Benares and Rangoon in 1935. Since this date several others have been reported, which, however, need not be spoken of in detail; they may be tabulated.

Place.	Date.	Cases.	Families.
Khargpur	1937, August 15–24th	184	38
Garpar	1937, August 24–28th	52	12
Kidderpore	1938, January 8–11th	6	1
Rangpur	1938, January 16–19th	65	24
Alamdangar	1938, January 21st–25th	32	15
Calcutta Medical School	1938, June 9–14th	13 (?18)	One group
Manirampur	1938, June 27th–July 4th	98	22
Suri	1938, July 1st–11th	20	9

Of these there are two which merit a few words, namely the Kidderpore and the Calcutta Medical School outbreaks.

The former was a small one involving the household of a merchant; there were fourteen members comprising, as regards messing, (1) The householder, his wife and three children; (2) Three male and three female servants; (3) Two shop-assistants and a motor-car driver. The second group only suffered, but all of them; they used the Bengalee diet and mustard oil exclusively for cooking-fat. Gastro-intestinal symptoms developed after a week, during which each had consumed about 8 oz. of the oil, and œdema was present in another week or ten days.

In the latter, the Calcutta Medical School residents comprised, as regards messing, four groups: (1) The patients, 155 in number; (2) The pathologist, nurses, cooks and compounders, 32 in all; (3) The house-surgeons, nine in number; and (4) The Resident Medical Officer. Among these, nine nurses, two cooks (and four others doubtful), the pathologist and one, possibly two, compounders were attacked. Altogether thirteen certain cases and five others doubtful, and all in group (2) which used the largest amount of mustard oil.

The Ætiology of Epidemic Dropsy

In the two years since the first publication of this work much study has been undertaken to solve the ætiology of epidemic dropsy. Lal, Ahmad, Roy and others in the years 1938–40 carried out several important investigations to determine the toxic factor responsible. The 'mustard oil theory' has been before the world at least since 1926, when Sarkar reported that symptoms resembling those of epidemic dropsy followed the consumption of mustard oil adulterated with *sialkata* or *katakar*, which is obtained from the seeds of an American weed, *Argemone mexicana*. Kamath, in the Surada, Ganjam, outbreak which dragged on from 1924 to 1926 and involved a hundred and two persons, implicated *odissimari* seeds, a synonym of Argemone.

Argemone seeds bear some resemblance to those of the mustard plant, *Brassica napus*. The chemical substance responsible for the pungency of the oil is allylisothiocyanate; this constituent of the oil is liberated from a glucoside, sinigrin, by the action of a ferment, myrosin, both of which are present in the oil. Allylisothiocyanate is a powerful irritant and would be likely to cause gastro-intestinal disturbance, which is an early symptom of epidemic dropsy. Experiments carried out by Lal, Ahmad and Roy on laboratory animals—rats, cats and monkeys—did not in any instance produce the symptoms of the disease, and human subjects took, for thirty days, food cooked in oil containing as much as 2517 mgm. of allyliosthiocyanate without any ill effects. This constituent of the oil may therefore be ruled out as the toxin responsible for the disease.

Chopra and his colleagues in 1939 tested on volunteers the effects of samples of oil obtained from houses where cases of epidemic dropsy had occurred. His subjects were divided into three groups: For one, the food was cooked in pure mustard oil to which known quantities of argemone oil were added; for the second, the food was cooked in samples of oil giving argemone oil reactions and implicated in natural outbreaks of the disease; the third group had a similar diet, but the food was cooked in mustard oil giving no reaction for argemone oil. Symptoms of the disease appeared in those receiving argemone oil, which seems to act cumulatively; provided a certain quantity is taken the symptoms appear after an interval, though consumption of the oil is stopped. Its toxic principle is destroyed by heating to 240° C., but not at 150° C. Chopra and his fellow-workers concluded that ingestion of the oil expressed from the seeds of *Argemone mexicana* can produce the symptoms of epidemic dropsy, but they cautiously add:

"Whether the condition produced is identical or not with the naturally-occurring epidemic dropsy cannot be definitely said at present, but there is no doubt that the use of oil containing argemone oil is harmful to man. There appears to be little doubt that consumption of adulterated oil produces symptoms which cannot be distinguished from those encountered in the naturally-occurring disease.

"From the evidence available it appears that the adulteration

. of mustard oil with argemone oil may or may not be intentional on the part of those who grow the mustard plant, or of those who express or sell the oil. The plant *Argemone mexicana* is widespread, its seeds bear a superficial resemblance to mustard seeds and may be harvested along with them. It is possible that, because oil can be obtained from the seeds of this plant, efforts are not made to exclude these seeds in the harvesting of mustard seeds."

Further experiments by Lal, Mukherji, Roy and Sankaran in 1939 were designed to determine whether the poisonous effects were due to deteriorated mustard seeds, to adulteration of the oil, or adulteration of the seeds. They found that seeds of *Argemone mexicana*, which resemble the black mustard seed, *Brassica napus*, impart the physical and chemical properties of toxic oil to mustard oil, and either accidentally or by deliberate adulteration these find their way into stocks of mustard seed and the expressed oil is present in sufficient amount in the final product to cause the symptoms observed in outbreaks of epidemic dropsy. Further, from oil of *Argemone mexicana* and from a proved toxic oil—but not from pure mustard oil—a white crystalline substance has been isolated which gives a characteristic colour change when nitric acid is added to the oil containing it.

Prevention would thus appear to be a simple matter, namely prohibition of the sale of argemone-containing mustard oil (and the adulteration is easily determined by the colour reaction), or heating it to 240° C., or 'fuming temperature,' for fifteen minutes, which practically destroys its toxicity.

The question of causation, however, is still not solved. The actual nature of the poison is not known, nor its mode of action. Argemone is a self-sown weed, a common contaminant of the mustard plant, and it seems strange that epidemic dropsy is not more widespread. It is, for instance, comparatively rare among the poorer Anglo-Indians who use mustard oil very largely for cooking—perhaps the heating reduces its toxicity. Again, rice, even sound rice, is generally thought to be bad for those suffering from epidemic dropsy, and it is further thought that those living on a diet into which rice enters largely are more susceptible to the disease, and that rice, therefore, does play some part, even if a subsidiary part only. It has been suggested that epidemic dropsy may be another example of 'conditioned toxicity'—" the toxic effect of a toxic substance being conditioned by the nature of the diet or the state of vitamin saturation of the subject "—other examples being selenium poisoning and high protein diet, and lead poisoning and vitamin C.

Investigations carried out yet more recently, in 1940, by Lal, Mukerji, Das Gupta and Chatterji, tend to throw further light on the problem. They consider the question under three heads: (1) To what extent seeds of *Argemone mexicana* are actually found in stocks used for pressing oil. (2) Whether a quantitative test could be developed to express the amount of toxic substance in a sample of mustard oil in terms of argemone oil. (3) How much toxic substance must be ingested to produce clinical symptoms.

To determine the first of these they obtained samples of the mustard

seed daily from a certain oil mill in Calcutta and found that three of the samples of *Brassica juncea* contained 5 per cent. of argemone seed. Rarely was a sample found to contain only one variety of seed.   In another series of samples from different oil-mills and stocks of seeds from wholesale dealers, amounts of argemone seed might constitute 10 per cent. or more.

The experiments directed towards the second question are intricate and call for delicate and expert technique, the description of which is beyond the scope of this work.   As for their third subject of research, investigations carried out on an epidemic at Satkhira show that many escaped because the amount consumed was just below that sufficient to give rise to symptoms.   The problem of determining the minimum quantity of argemone oil in mustard oil the ingestion of which will produce symptoms may be tackled in various ways, such as comparing the toxic effects with analysis of the oil, or by tracing an oil containing known amounts of reacting substance to the consumers and observing developments among them, or by concurrent study of the oil and of the persons consuming it and finally determining the reacting substance of samples of oil used in human experiment, the preparation being given in food.   Their studies pointed to the conclusion that oil which contains less than 1 per cent. argemone oil, or oil representing 1 mgm. of the reacting substance taken daily for twenty days is not likely to produce clinical symptoms; in other words, the presence of less than 1 per cent. of argemone oil in mustard oil will not result in causing demonstrable symptoms under the usual conditions of consumption of the oil in Bengal.

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